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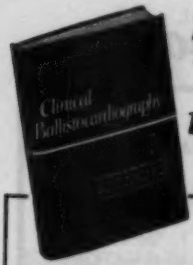

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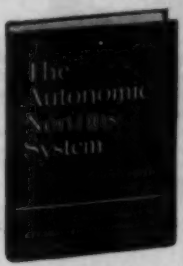

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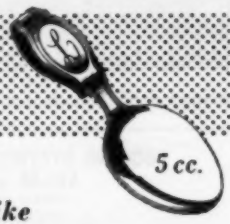

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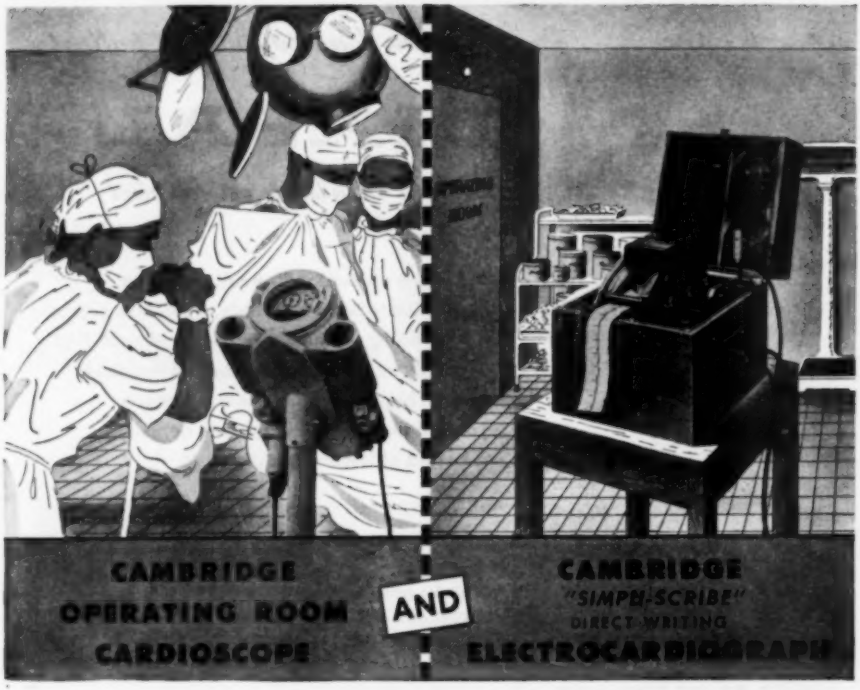

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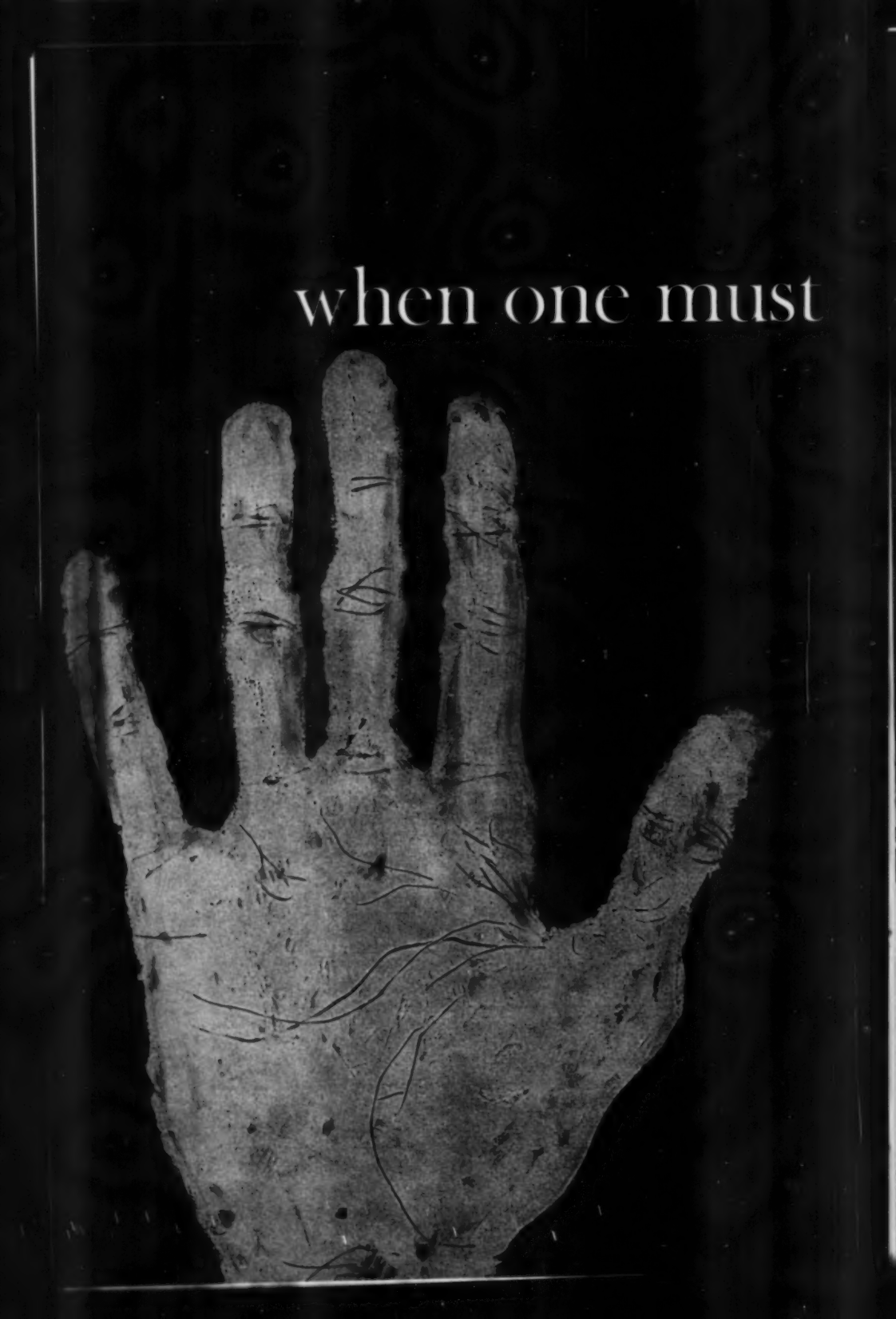

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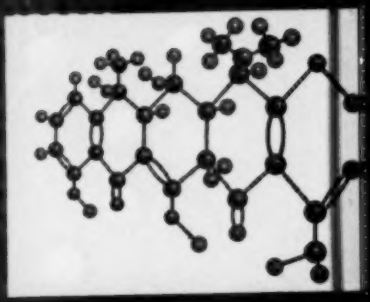

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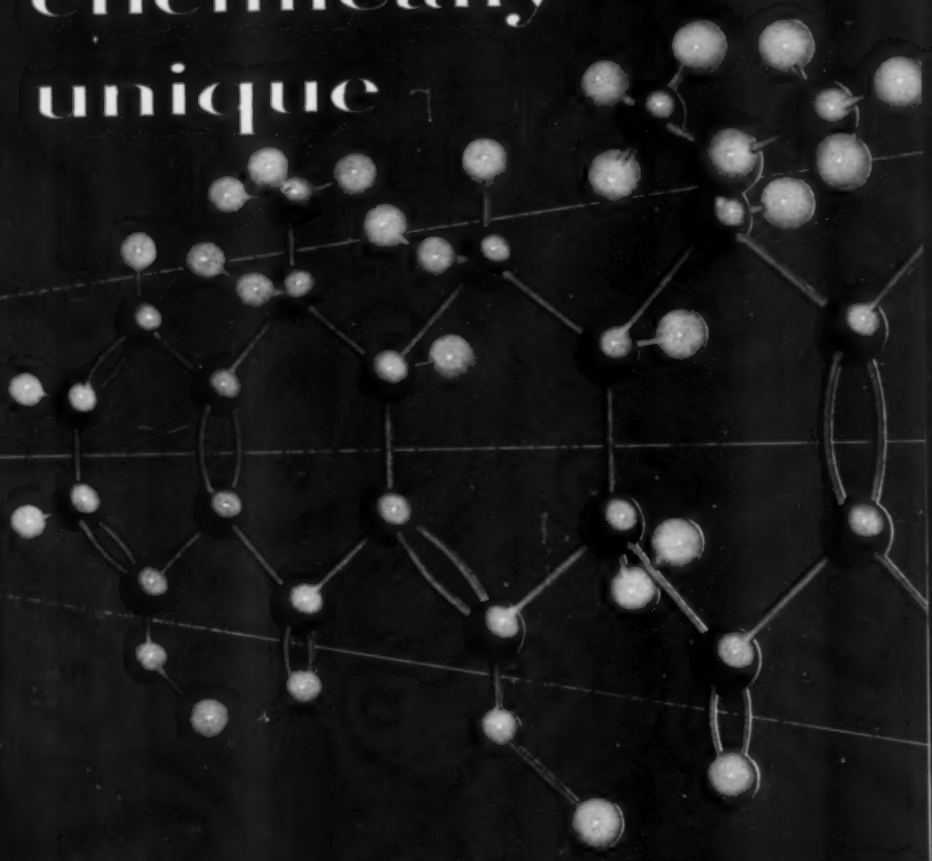

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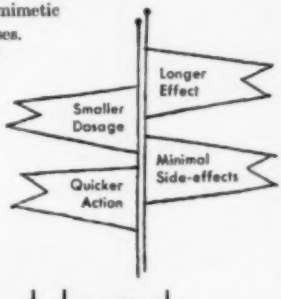

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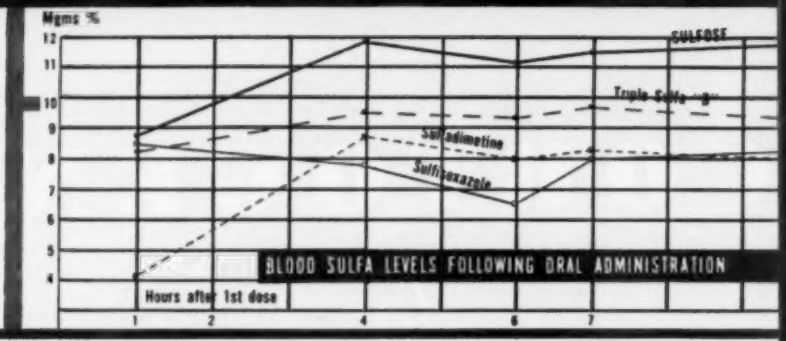

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—higher, more prolonged blood levels than any other sulfa preparation studied—single or combination[1]

—excellent tissue distribution—spinal fluid levels superior to those produced by single sulfonamides

—superior antibacterial potency, because of potentiating action of sulfonamide mixture

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—higher solubility in *acid urine* than single sulfonamides (with acetyl derivatives), minimizes danger of renal blockage

—minimal tissue toxicity; blood cell damage, nausea, vomiting, etc., occur less frequently than with single sulfa therapy

3. *SULFOSE is a triple sulfa*

—danger of sensitization is minimal because each sulfa component is given in low dosage. Sensitization becomes more frequent when daily doses of a sulfa drug exceed 4 Gm.[2]

4. *SULFOSE is more convenient*

—low daily dosage requirement (4 Gm. for adults) means minimal interference with rest

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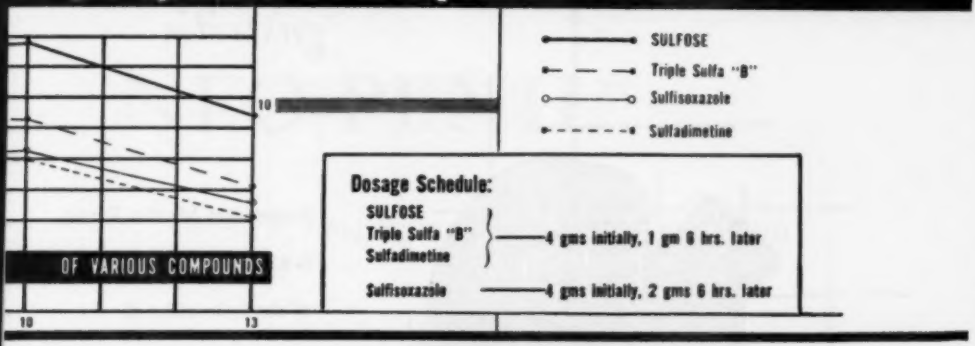

5. *SULFOSE is more economical*

—costs less per dose than modern single sulfas; also, fewer doses are needed

6. *SULFOSE is palatable*

—insures acceptability to patient

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Supplied: Bottles of 1 pint.
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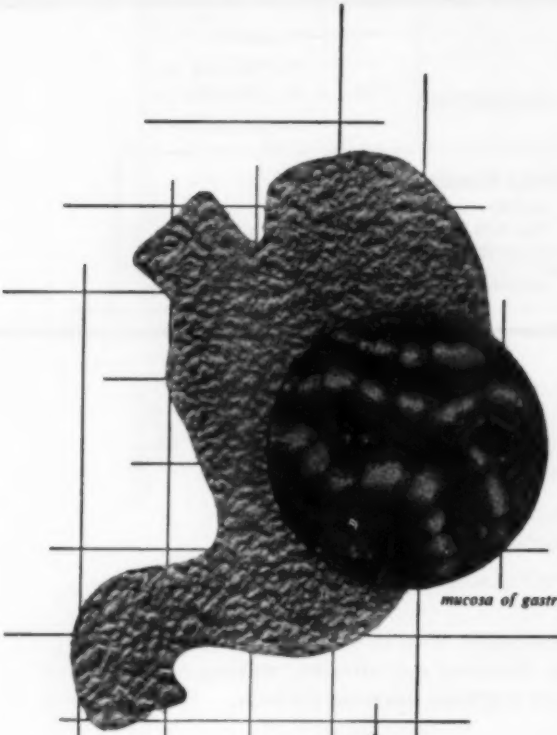
Wyeth

1. Berkowitz, D.: To be published.
2. Lehr D.: New York State J. Med. 50:361 (June 1) 1950.

for

gastritis



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"This compound appeared to have a unique value in respiratory infections due to gram-positive bacteria."[1]

Bibliography: 1. Barach, A.L., et al.: Bull. New York Acad. Med. *28*:353 (June) 1952.
2. Flippin, H.F., et al.: Report distributed at the Chicago Session of the A.M.A. (June) 1952.
3. Segal, M.S., et al.: GP, in press.

'Neo-Penil' is available at retail pharmacies, in single-dose, silicone-treated vials of 500,000 units. *Full information about 'Neo-Penil' accompanies each vial,* or may be obtained by writing to:

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CHLORINE	900 mg.	MANGANESE	0.4 mg.	BIOTIN	0.03 mg.	*RIBOFLAVIN	2.0 mg.
COBALT	0.006 mg.	*PHOSPHORUS	940 mg.	CHOLINE	200 mg.	*THIAMINE	1.2 mg.
*COPPER	0.7 mg.	POTASSIUM	1300 mg.	FOLIC ACID	0.05 mg.	*VITAMIN A	3200 I.U.
FLUORINE	3.0 mg.	SODIUM	560 mg.	*NIACIN	6.7 mg.	VITAMIN B_{12}	0.005 mg.
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*IRON	12 mg.						

*PROTEIN (biologically complete)	32 Gm.
*CARBOHYDRATE	65 Gm.
*FAT	30 Gm.

*Nutrients for which daily dietary allowances are recommended by the National Research Council.

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1. *Seley, S. A.: Am. J. Dig. Dis. 13:238 (July) 1946.* 2. *Rossien, A. X.: Rev. of Gastroenterol. 16:34-52 (Jan.) 1949.* 3. *Rossien, A. X. and Victor, A. W.: Am. J. Dig. Dis. 14:226-229 (July) 1947.* 4. *Batterman, R. C. and Ehrenfeld, I.: Gastroenterol. 9:141 (August) 1947.*

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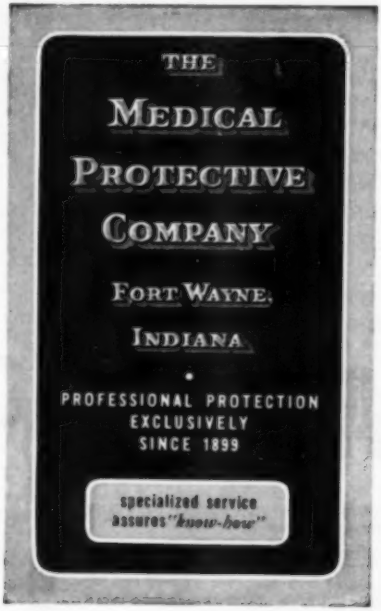

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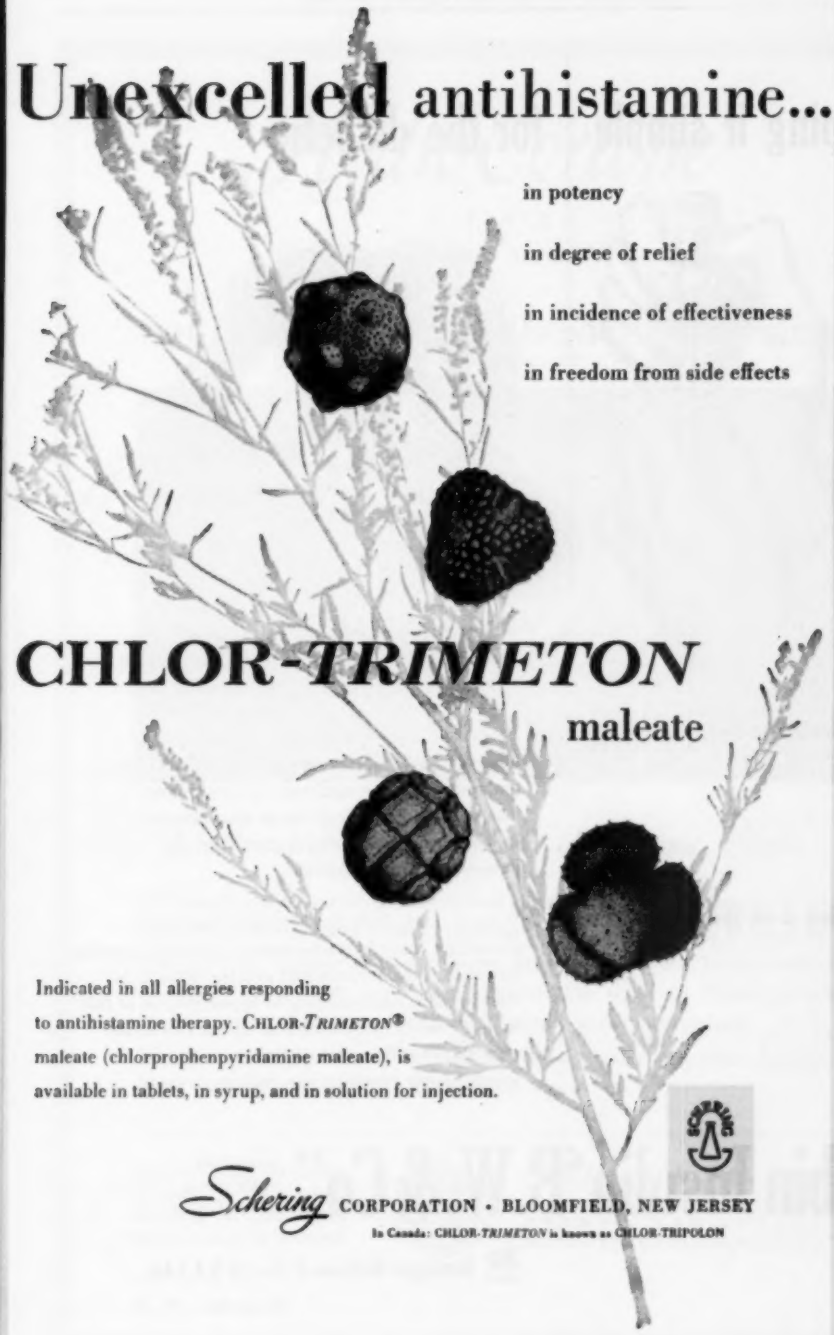

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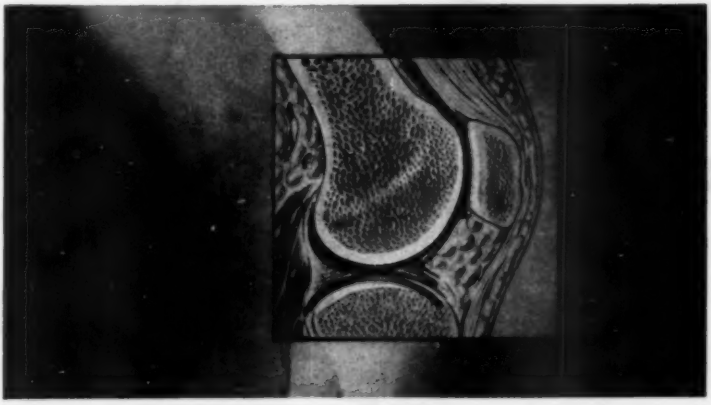

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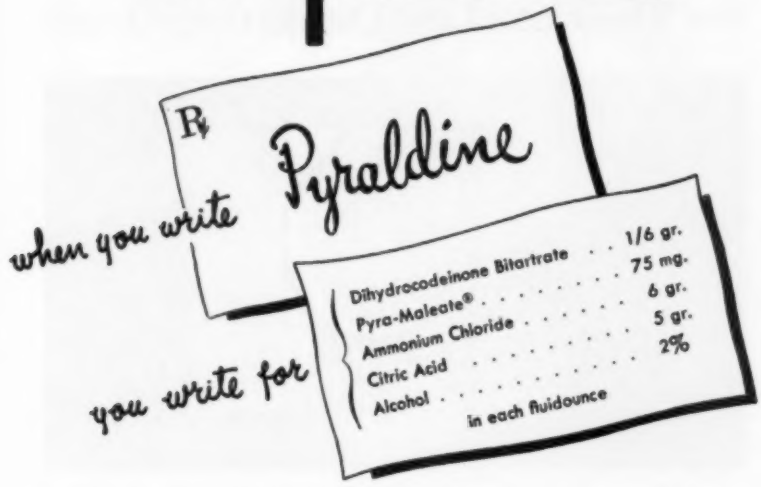
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*McCLINTOCK, J. C., AND LYONS, J. J. A. M. A. STATE J. MED. 51:1403, 1951

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1. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: N.Y. State J. Med. 52:2012 (Aug. 15) 1952.

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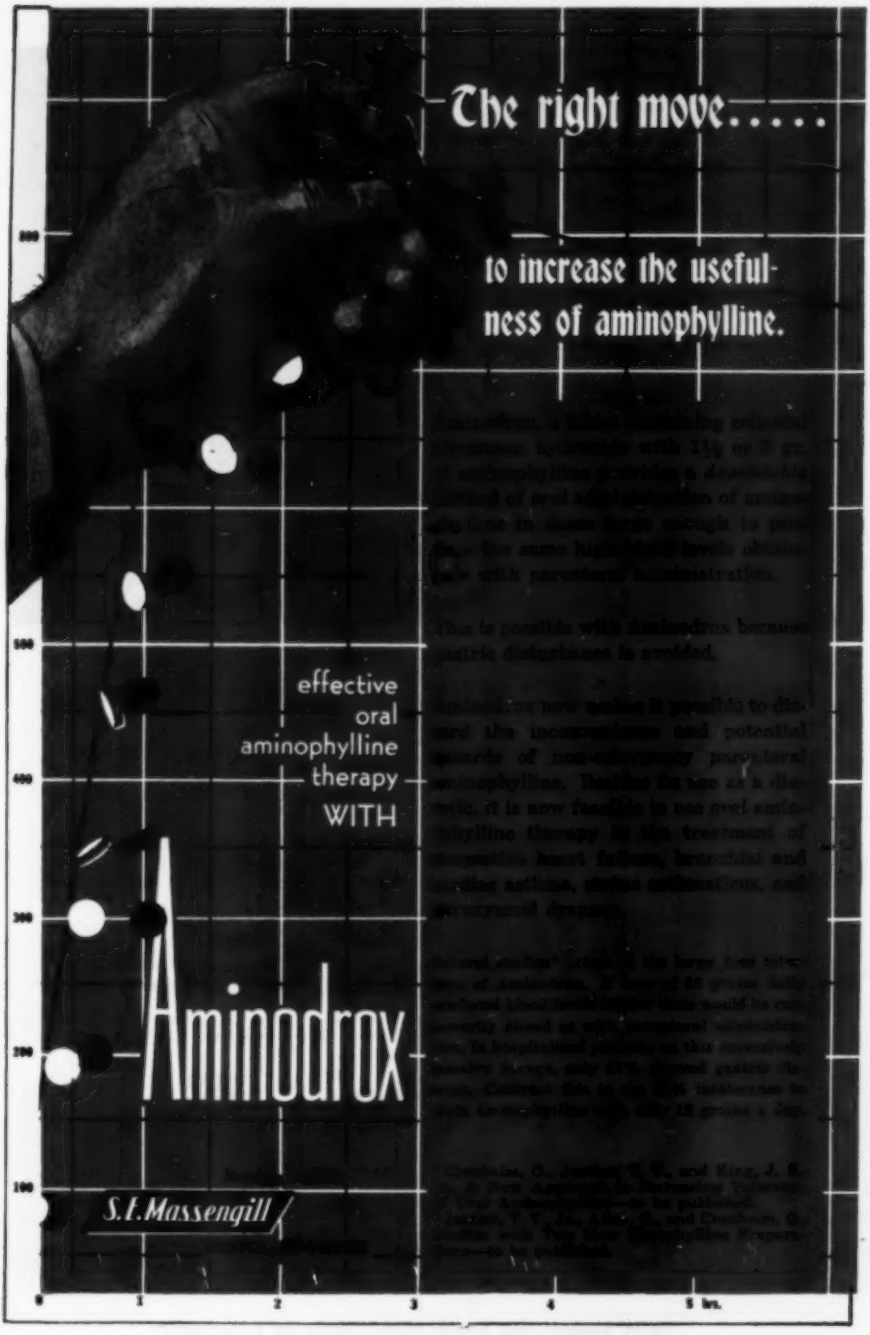
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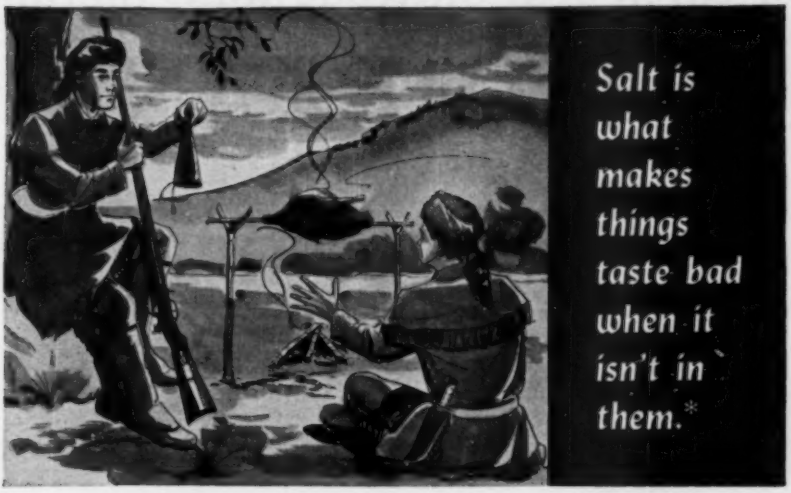

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1. Merryman, M. P.: The Use of the Low Sodium Diet. South Dakota Jour. Med. & Pharm., 2:57, Feb., 1949.
2. Keller, E. K.: The Treatment of Essential Hypertension. Connec. Med., Aqua. Assn., 61:273, Sept., 1949.

*Author unidentified. From Menchen, H. L.: A New Dictionary of Quotations. New York, Alfred A. Knopf, 1949, p. 1007.

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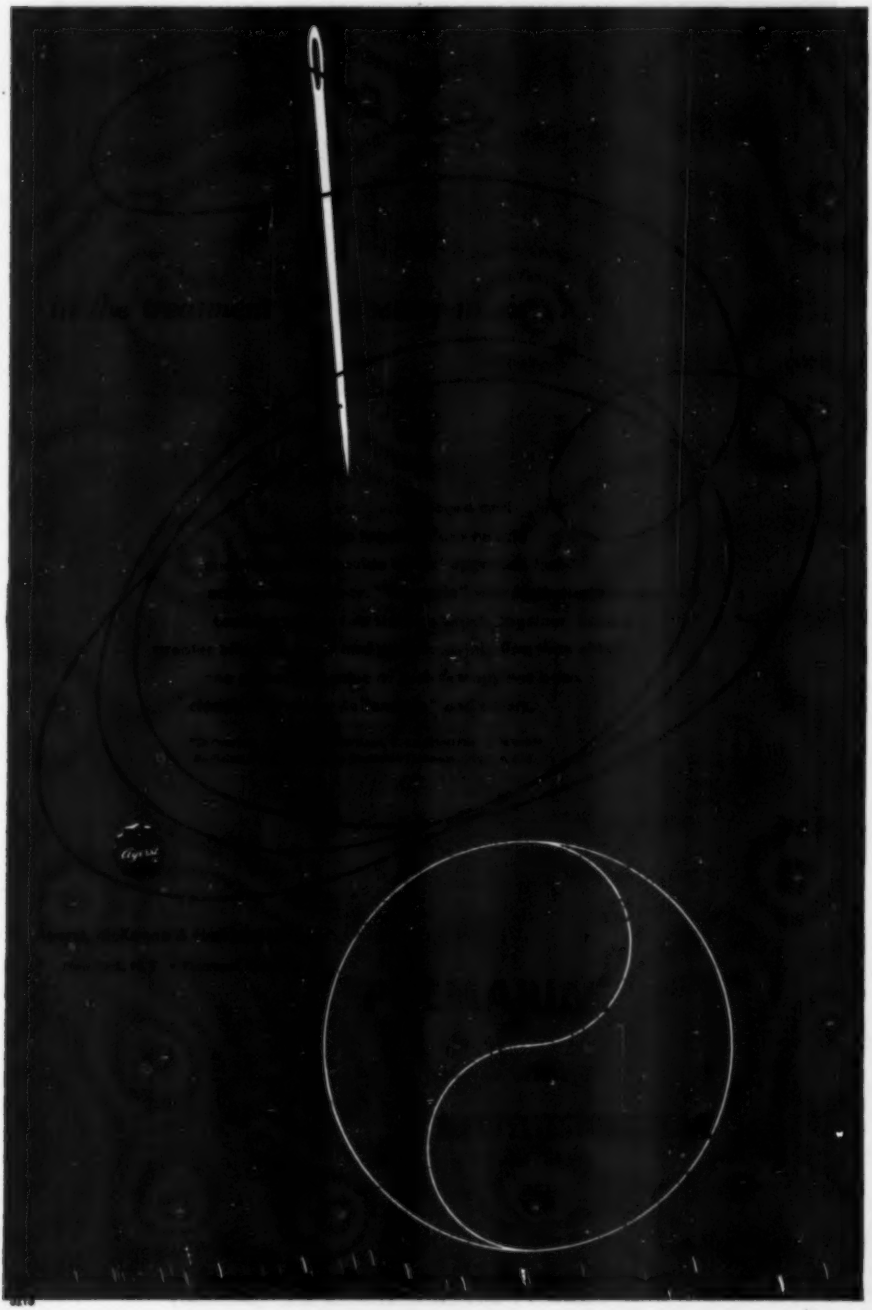

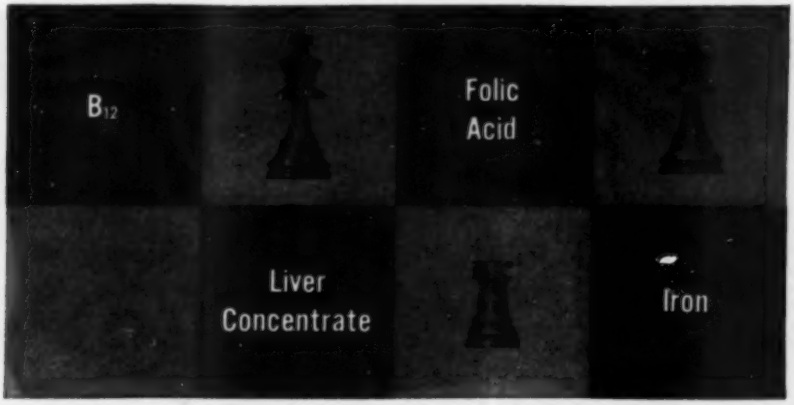

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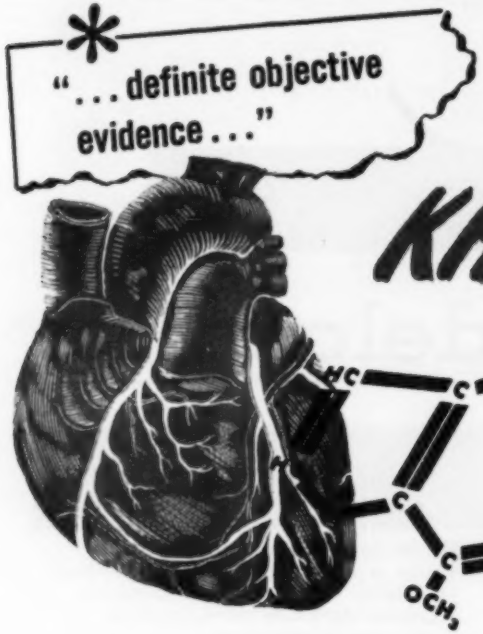

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**Nalefski, L. A., et al: The Use of Crystalline Visammin in the Treatment of Angina Pectoris, Circulation 5:851 (June) 1952.*

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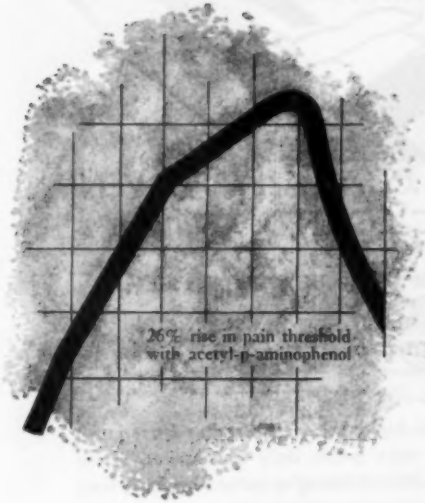

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*Talkov, R. H., Ropes, M. W., and Bauer, W.: *The Value of Enteric Coated Aspirin.* N.E.J. Med. 242,19 (Jan. 5) 1950.

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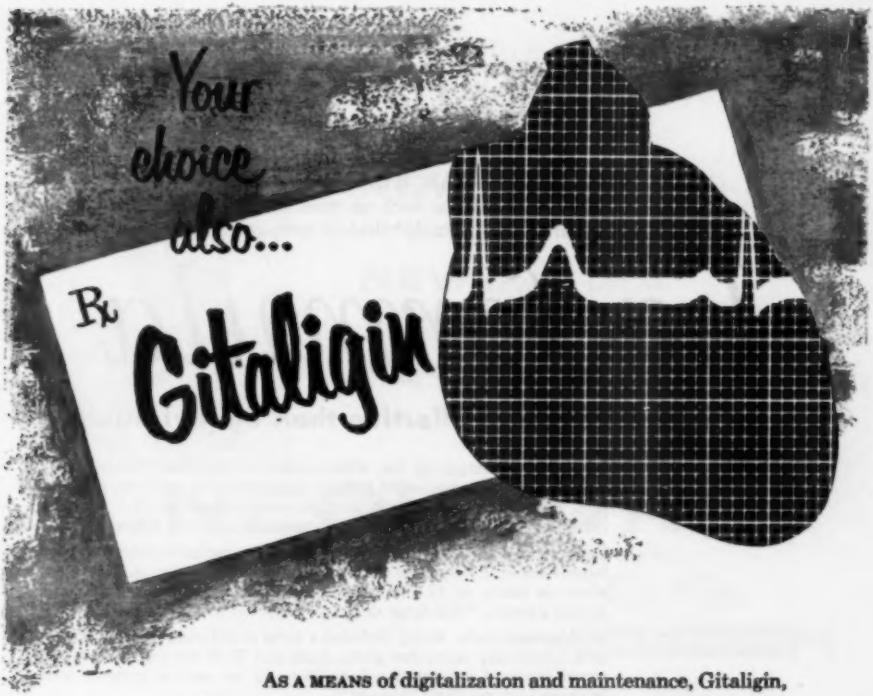

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1. Batterman, R. C.; DeGraff, A. C.; Gutner, L. B.; Rose, O. A., and Lhowe, J.: Studies with Gitalin (amorphous) for the Treatment of Patients with Congestive Heart Failure, Am. Heart J. 42:292-307 (Aug.) 1951.

2. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: The Therapeutic Range of Gitalin (amorphous) Compared with other Digitalis Preparations, Circulation 5:201-207 (Feb.) 1952.

3. Nalefski, L.: Personal Communication

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1. Cass, L. J., and Wolf, L. P.: Gastroenterology *20*:149 (Jan.), 1952.
2. Berberian, D. A., Pauly, R. J., and Taintor, M. L.: Gastroenterology *20*:143 (Jan.), 1952.

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Ross, M.: Am. Pract. & Dig. Treat. 2:955 (Nov.) 1951
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ANNALS OF
INTERNAL MEDICINE

VOLUME 37 OCTOBER, 1952 NUMBER 4

A DISCUSSION OF THE CONCEPT OF CARDIAC FAILURE IN THE LIGHT OF RECENT PHYSIOLOGIC STUDIES IN MAN *

By ANDRÉ COURNAND, *New York, N. Y.*

IN any line of scientific investigation it is profitable to pause from time to time to reëxamine concepts in the light of new experience. Quoting J. B. Conant [1] freely, the value and significance of a conceptual scheme in science are not so much that it constitutes "a quest for certainty," but rather that it "breeds new experiments which in time generate new ideas." The fruitfulness of such an intellectual endeavor in medicine is, in addition, measured by its consequences in terms of the practical applications to which it leads, among which progress in therapy stands foremost.

In the last 10 years the development of new and more accurate methods of clinical investigation has stimulated studies of the circulation in normal man and in patients with different types and in various stages of heart disease. A detailed description of these methods and an analytic review of these studies up to 1951 have been presented in a recent monograph.[2] Measurements of total and individual visceral blood flows, of total and pulmonary blood volumes and of intracardiac and intravascular blood pressures may now be obtained, for the most part accurately, repeatedly and simultaneously under controlled conditions. Indeed, such studies have been conducted (1) in the basal metabolic state and during the steady state of an exercise; (2) under the influence of a rapid intravenous infusion, of induced anoxia and of a rapidly acting drug, such as a digitalis glycoside, quinidine,

* Presented as the John Phillips Memorial Lecture at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 23, 1952.

From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Cardio-Pulmonary Laboratory of the First Medical and Chest Services (Columbia University Division), Bellevue Hospital, New York, N. Y.

The work reported here was aided by a research grant (PHS Grant H-833 (C)) from the National Heart Institute of the National Institutes of Health, Public Health Service, with additional support from the Life Insurance Medical Research Fund.

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etc.; (3) before and after prolonged cardiocirculatory therapy such as full digitalization, repeated phlebotomies, oxygen therapy, and (4) following surgical procedures devised for the relief of intracardiac valvular stenoses or extracardiac pericardial constriction. Besides providing valuable diagnostic and therapeutic information in individual cases, well planned studies may contribute to the understanding of general problems, among which cardiac failure is our immediate concern.

Since Hope and Stokes, two main theories of cardiac failure have been expounded: in one, emphasis has been laid upon the upstream effects of the failing heart, i.e., venous congestion; in the other, upon its downstream effects, i.e., reduction in cardiac output. In addition, chronic venous congestion has been considered by Starr [3] as distinct from cardiac failure. In the historical development of these concepts, known as "forward" and "backward" failure, animal experiments have played an important part in the formulation of certain principles governing the cardiac performance under changing conditions. Both by implication and directly, consideration will be given in this presentation to some of the basic knowledge derived from the work of various physiologists. This work has been reviewed recently and discussed brilliantly by Wiggers.[4]

There is no doubt, however, and I quote from Wiggers,[5] that "deductions regarding cardiac behaviour derived from controllable acute experiments on the dog's heart can be transferred to the human heart, provided that proper reserve and caution are exercised." Indeed, reserve and caution are required, since chronic cardiac failure as observed in man, with its variety of forms and complexity of mechanisms, is not as yet reproducible in dog. Furthermore, in the attempts of Starr,[6] Landis,[7] and Roos and Smith [8] to create acute cardiac failure in dogs, hemodynamic data were of a limited scope as compared to data obtained in human studies. It must be emphasized also that investigations in man have a distinct advantage over animal experiments in providing some simple and easily recognizable patterns of cardiac failure in selected cases.[9, 10] Their identification may serve as a starting point in unraveling the more intricate processes encountered. Furthermore, in studies in man, under the influence of appropriate tests or therapy, one or a few variables in the hemodynamic picture may be altered or the state of failure completely reversed under observation.

An understanding of the altered performance of the ventricular pump in cardiac failure, from which stems a series of readjustments in the other component parts of the circulation, requires a knowledge of the factors involved in ventricular contraction and output and in the distribution of blood volume and regional blood flows in the normal circulation. We shall therefore briefly define these factors.

Most physiologists agree now that the mechanism of contraction of both ventricles is controlled (1) by the innate physiologic characteristics of the myocardial fibers, the resting length and the contractile power of which may

be affected by local factors such as coronary flow, nervous stimulation, metabolites and chemical constituents of the blood, including hormones and specific drugs; (*2*) by the venous inflow which regulates the initial length of the fibers before they start to contract, and (*3*) by the arterial resistance which influences the tensions developing in the contracting fibers as systole progresses and thereby the mode and volume of ventricular ejection.

A simplified statement of these mechanisms is as follows: (*a*) The venous inflow controls the filling and arterial resistance the emptying of the ventricular cavity, the contractibility of the wall of which may be influenced by local myocardial factors. (*b*) Since neither fiber length nor the capacity of the ventricle at the beginning of systole is measurable in man, measurement of the initial tension or of the end diastolic pressure is our best means

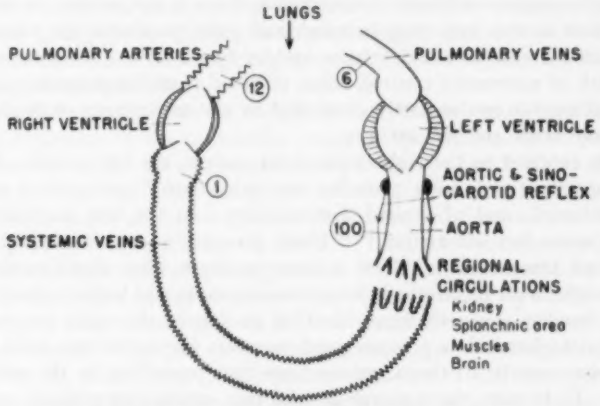

FIG. 1. Schematic representation of the circulation.
This scheme contrasts differences in the capacity and in the volume distensibility between the various component parts of the circulation. Figures within small circles refer to mean blood pressures expressed in mm. Hg.
For description see text.

of their approximation. (*c*) It must be pointed out also at this time that, in partly controlling the postsystolic residual volume of blood in the ventricles, variation in arterial resistance has an indirect effect on the filling volume and pressure during the succeeding diastole as long as the venous inflow remains unchanged. This interrelation is one of several which will retain our attention in this discussion.

Although both ventricles have common factors controlling their contraction under normal circumstances, each ventricular pump and its respective venous inflow and arterial outflow system operate in a strikingly distinct manner. Figure 1 illustrates a scheme of the circulation stressing these differences which originate from structural and physiologic characteristics:

1. The systemic veins, including the right atrium, are incompletely filled and the approximately 55 per cent of the total blood volume which they contain encroaches little upon their margin of distensibility; hence venous blood pressure here is low. Furthermore, additional amounts of blood may accumulate in this system without a significant rise in pressure. With its small muscle mass and great volume distensibility, the right ventricle is able to accommodate increased venous inflow with only small increments of the end diastolic pressure,[11] and to transfer this blood into the low resistance pulmonary arterial system. Indeed, the short pulmonary arterial tree and its related capillaries are readily distensible, the latter more than the former, and the approximately 5 per cent of the total blood volume herein contained leaves a fairly large potential of distensibility. The pressures in the pulmonary artery, therefore, are low and the pulse pressure is small.[12] Inasmuch as under ordinary circumstances there is no arterial or arteriolar constriction in this bed, rises in mean and pulse pressures are related to a significant increase in blood volume and/or blood flow. As a consequence of the lack of vasomotor control, efflux of blood from the pulmonary arterial and capillary systems is partly controlled by the movements of blood in the pulmonary veins and left atrium.

2. In contrast to the right veno-atrial system, the left is very short, of small capacity (containing probably not more than 5 per cent of the total blood volume), and of limited distensibility. In the less distensible pulmonary veins and left atrium [13, 14] blood pressure is somewhat higher, and with small increments in blood volume pressure rises significantly. The left ventricle, with its relatively larger muscle mass and lesser volume distensibility, handles a venous input identical to that of the right ventricle at a somewhat higher inflow pressure, and transfers blood into the aorta against a resistance nearly 10 times greater than that prevailing in the pulmonary artery. To be sure, the systemic arterial tree, containing probably not more than 20 per cent of the total blood volume, has a small margin of distensibility: therefore, mean pressure is much higher and pulse pressure larger in the aorta than in the pulmonary artery. These pressures, however, normally vary little, despite potentially large variations in ventricular output, because they are under the control of a most remarkable set of reflexes, the rôle of which in the maintenance of circulatory homeostasis is unique. These reflexes originate in the walls of the arch of the aorta and of the carotid sinus,[15] where receptors extremely sensitive to changes in tension of the vascular wall during left ventricular ejection activate nervous impulses. These are transmitted through a complex afferent and efferent pathway and finally regulate the tonus of the muscular wall of the systemic arterioli. Hence vasomotor action, controlling the efflux of blood from the aortic system, is the source of many interrelated and compensatory effects: (*a*) by its regulation of pressure in the aorta, coronary flow as well as ventricular outflow is influenced; (*b*) by its selective effect upon regional vascular resistances, the total left

ventricular output is distributed in various proportions to regional circulations, i.e., mainly to the kidney, the splanchnic area, the brain and the muscles; (*c*) by its modification of the capacity of the arterial tree, blood transfer into the capillary and venous systems is reduced or enhanced and may eventually affect the venous inflow into the right ventricle.

How, then, is the structural and physiologic design of the circulation which we have thus briefly sketched interfered with when one or both ventricular pumps fail? How is blood redistributed in both circuits under the influence of potential dynamic imbalance between both ventricles—what has been called ventricular heterodynamism—and according to the available margin of distensibility of the veins and arterial systems of each? Is the homeostatic mechanism which maintains a relatively stable aortic pressure beneficial in such a situation, or does it become a hindrance and the source of further embarrassment to the circulation? Such are some of the most important questions to consider in formulating a hemodynamic concept of cardiac failure. But first we have to define cardiac failure, and to analyze its modes of development.

Hemodynamically, cardiac failure is best defined as a state in which there is reduction of the contractile power of the ventricular muscle in the face of an increasing filling pressure. According to Starling's experiments, this reduction occurs when the fibers are stretched beyond a critical point. The intimate cause of the mechanical inefficiency of the muscular fibers developing beyond this critical point seems to reside, in most instances, not in a reduced supply of oxidative energy, but in the inability of the fibers to transform this oxidative energy into useful work, as a result of ineffective biochemical processes involving carbohydrate metabolism and the specific contractile proteins.[16] Be that as it may, the reduction in contractile power is essentially the result either of a primary alteration of the myocardial fibers or of an overloading of the venous return associated with hypervolemia. Both factors may be present singly or combined in various proportions, according to the nature of cardiac lesions and the stage of evolution of cardiac failure. In any event, a relative reduction in cardiac output and the associated increase in the end diastolic filling pressure, and therefore in the volume of blood left in the ventricle at the end of systolic ejection, are the hemodynamic earmarks of the failure of the ventricular pump. Indeed, the output of the failing heart at rest, under basal metabolic conditions, is not necessarily less than that of a normal heart in the same state: the reduction in output is not always absolute, but it is relative to that existing immediately preceding the onset or following the relief of failure—other variables, notably the blood volume, remaining the same. We are therefore in accord with the thesis defended by Harrison,[17] namely, that the cardiac output in failure may be low, normal or elevated, depending upon the nature of the cardiac lesion, the degree of hypervolemia, and the presence of generalized hyperemia and of rare and abnormal states such as those caused by

severe anemia and thyrotoxicosis; and hence, that it is contingent upon a multiplicity of factors operating before failure sets in. But consideration of the cardiac output alone is not sufficient to decide whether cardiac failure is present, since it may be low during compensation. It must then be agreed with D. W. Richards that consideration of intracardiac pressures is far more important.[18] Cardiac failure may also become manifest only during increasing physical activity. In such instance, the increase in cardiac output is less than it should be with a normal heart, with respect to both the rise in intracardiac pressure and the metabolic demand of the body.

We may now discuss in general the nature of the circulatory readjustments which follow the failure of one or both ventricles. These readjustments consist (1) in a redistribution of blood volume from one part of the circulation to another, and (2) in the re-apportioning of visceral and regional blood flows.

The redistribution of blood from the arterial to the venous system is caused by three factors of unequal importance: (*a*) temporary excess of arterial outflow over venous inflow; (*b*) diminution of the capacity of the systemic arterioles following reflex arteriolar constriction, and (*c*) ventricular heterodynamism. The first two factors are relatively unimportant, since they cause the mobilization of only a small volume of blood in the systemic veins. On the other hand, the maintenance by one ventricle of its output while the other ventricle fails is potentially of great importance, since it causes blood to be moved ultimately into the venous system draining into the failing ventricle, and thus increases its venous inflow pressure and its end diastolic pressure. Hence the function of the failing ventricle is further compromised until a new and precarious dynamic equilibrium between both ventricular outputs is reëstablished. However, in judging the effects of ventricular heterodynamism upon the severity of venous congestion, it is essential also, as we shall consider presently, to know which ventricle is failing and what degree of hypervolemia, if any, is present.

The problem of redistribution of visceral blood flows under the selective action of systemic arteriolar constriction will not detain us too long, since it has been fairly well elucidated by the studies of Merrill [19, 20] and of Stead and his school.[21, 22] Suffice it to state that the reduction in renal blood flow is proportionally much greater than that of the splanchnic and cerebral circulation, and that severe renal ischemia has been shown to cause salt and water retention and therefore to play some part in an eventual increase of plasma volume. The homeostatic mechanism whereby the aortic pressure remains constant in the face of a reduction in cardiac output leads to the maintenance of an adequate perfusion pressure into the coronary circulation; but since the prolongation of the reflex mechanism causes a persistent reduction of the renal blood flow, it may be considered to be a source of embarrassment to the heart by eventually promoting hypervolemia, and thereby increasing the circulatory load.

It is pertinent to my discussion that I should illustrate now some of the hemodynamic patterns encountered in the study of pure and combined forms of left and right ventricular failure. For this purpose I have selected four cases studied before and after intravenous injection of digoxin by Dr. Ferrer and Dr. Harvey in my laboratory.

Such studies are particularly rewarding in early and pure left ventricular failure observed in hypertensive and ischemic heart diseases, since their

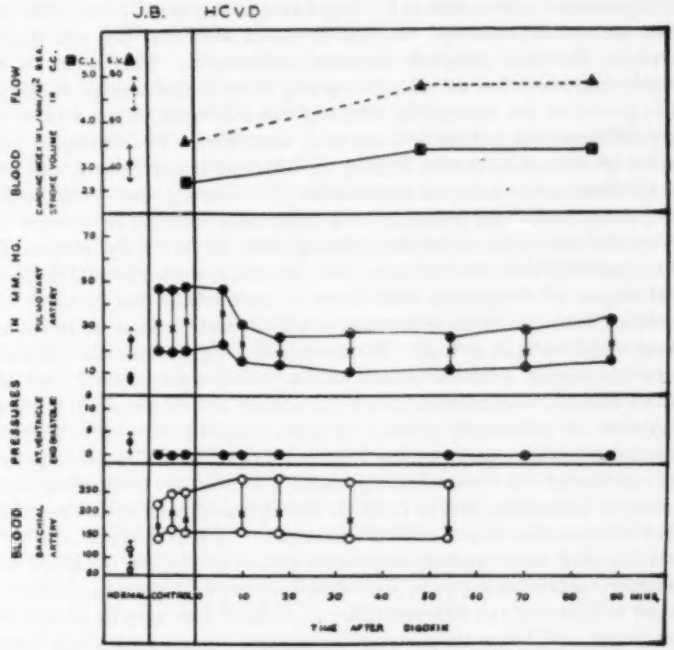

FIG. 2. Hemodynamic measurements in a case of hypertensive cardiovascular disease with early manifestations of left ventricular failure.

The normal mean values and the approximate range of variations are plotted in the first vertical column; the first series of measurements during the control period are plotted in the second vertical column, and the measurements after intravenous injection of 1.5 mg. of digoxin in the next vertical column.

For discussion see text.

results can be interpreted simply and unequivocally. Observations made in such a case are presented in figure 2. The first series of measurements in this case of pure left ventricular failure, if compared to normal values, show (*a*) a moderate reduction in cardiac output and stroke volume; (*b*) an elevation of all pressures in the pulmonary artery; (*c*) a normal end diastolic

pressure in the right ventricle and, obviously, (*d*) a considerable rise in all systemic arterial pressures. The measured total blood volume was just above the upper limit of normal.

We can now follow a series of striking changes induced by the intravenous administration of digoxin from the time of injection until 90 minutes later. They consist in (*a*) a rapid fall of all pressures in the pulmonary artery, including the pulse pressure; (*b*) an increase in cardiac output and stroke volume which amounted, respectively, to 22 per cent and 53 per cent of their previous values; and (*c*) a slight rise of the systolic and pulse pressure in the systemic artery. It will be noted also that the end diastolic pressure in the right ventricle remained unchanged. This series of data obviously indicated that all changes sprang from modifications of the contractile power of the myocardial fibers of the left ventricle, and from temporary differences in output between both ventricles. The following reconstruction of the serial events leading to left ventricular failure and to its relief involves a minimum of speculation: (1) During the development of failure, either under the influence of a temporary increase in venous input or in arterial resistance so common during daily activities, the altered fibers of the hypertrophied and ischemic left ventricle were stressed beyond a critical degree of elongation, their force of contraction was reduced under the existing load, and thus a decrease in output and increase in postsystolic residual blood volume ensued. Meanwhile the right ventricle maintained its previous output, since its venous inflow was not yet reduced, and blood therefore started to accumulate in the pulmonary circulation, with the resulting increase in pulmonary arterial systolic, diastolic and pulse pressures; simultaneously, pulmonary venous congestion developed, the filling pressure of the overloaded left ventricle progressively stepped up, promoting further reduction in its output, until a more or less dynamic equilibrium was finally reached between the output of both ventricles. (*2*) Conversely, during the restoration of a more normal contractile power of the left ventricle under the salutary action of digoxin, the whole sequence of dynamic events was reversed in favor of the left ventricle; its output now was in excess of its venous input, and hence its postsystolic residual volume and filling pressure decreased; progressively the excess of blood in the pulmonary vascular system was pumped out in successive steps until a new and stable equilibrium was reëstablished between the output of both ventricles, this time at the higher level controlled by the left ventricle. Because of their importance in our demonstration, the significance of variations in pulse pressure and diastolic pressure in the pulmonary artery must be emphasized: (*a*) In the presence of a low stroke volume, the large pulse pressure observed during the first studies reflected the storage of blood in the pulmonary arterial system, with the attendant reduction in its margin of distensibility; during the second studies, following digoxin therapy, the decrease in pulse pressure in the presence of a higher stroke volume indicated that the blood previously

stored in the pulmonary arterial system had been mobilized. (*b*) On the other hand, it has been shown that in the range of pressures observed, diastolic pressure in the pulmonary artery varies parallel with the end diastolic pressure in the left ventricle; this is correct only if the situation is not complicated by an increase in resistance in the small pulmonary vessels, a most unlikely hypothesis in this instance, unless one assumes pulmonary arterial constriction before the action of digoxin took place.

With the next case I should like to illustrate a very interesting type of right ventricular failure associated with a considerable increase in total blood volume. The pattern that it exemplifies has been referred to as high output failure,[23] and is observed in cases of chronic pulmonary emphysema with severe arterial hypoxia, carbon dioxide retention, marked polycythemia and the clinical manifestations of right heart failure.

Hemodynamic data presented in figure 3 show (*a*) the considerable increase above normal of both cardiac output and stroke volume, (*b*) the marked rise in all pulmonary arterial pressures, (*c*) the high end diastolic pressure in the right ventricle, and (*d*) the normal systemic arterial pressures. On the basis of this single study the explanation could be offered that the hemodynamic pattern fits very well circulatory changes related (*a*) to a severe degree of chronic venous congestion, since the blood volume was considerably increased, and (*b*) to a generalized hyperemia, possibly due to arterial hypoxia, since the cardiac output was high and the systemic pressures were normal. Failure of the right ventricle, however, is clearly demonstrated by the measurements made after intravenous digoxin therapy, as they indicate the rise in cardiac output and stroke volume, reaching, respectively, 16 per cent and 22 per cent of their previous value, and a return of the end diastolic pressure in the right ventricle to a normal level. Since the mean pressure in the pulmonary artery did not vary significantly, the work of the right ventricle obviously increased. No alternative explanation than the improvement of the contractile power of an overloaded ventricle can be offered for these changes unless one returns to the hypothesis, long abandoned by McMichael himself,[24] of a veno-dilator effect of the digitalis glycosides.

It should be noted also that there was an increase in pulse pressure in the pulmonary artery characterized by a rise in the systolic pressure, probably reflecting the increased stroke volume in a still restricted pulmonary vascular bed. The absence of a fall in pulmonary artery diastolic pressure strongly suggests that there was little change in the left ventricular filling pressure, and hence that the left ventricle had not been in failure.[10]

In this case, the blood volume was reduced following the first series of studies by repeated phlebotomies and also by relieving the severe arterial hypoxia under appropriate therapeutic methods. As shown in a second and third series of studies done at an interval of a few weeks and 16 months after the patient had resumed daily activities, the blood volumes were main-

tained at a lower level but plethora was still present. The other hemodynamic data were identical on both occasions: (*a*) the cardiac output, the stroke volume and the pulmonary arterial pressures were all reduced, and near the upper limit of normal; (*b*) the end diastolic pressure in the right ventricle was lower, and (*c*) the systemic arterial pressures were unchanged. All these findings were then compatible with a degree of plethora not great

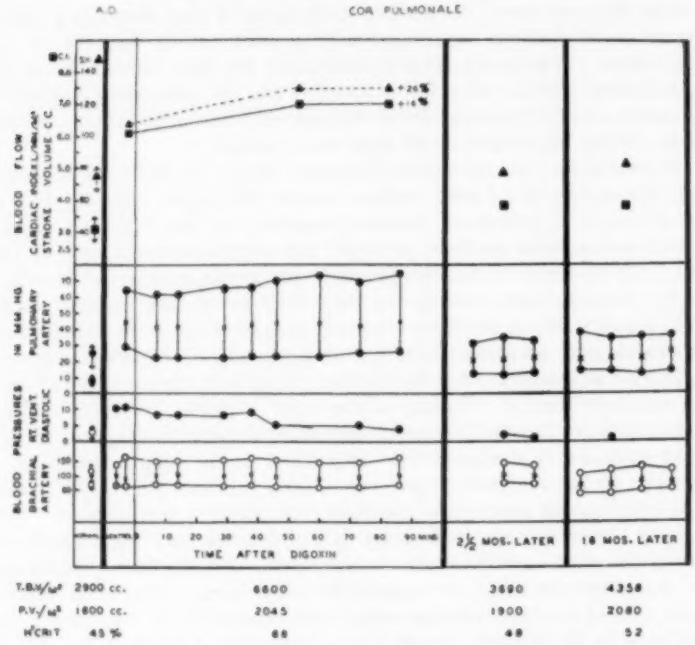

FIG. 3. Hemodynamic measurements in a case of chronic pulmonary emphysema with severe anoxia, considerable hypervolemia and right ventricular failure.

In the second and third vertical columns are plotted the measurements before and after intravenous injection of 1.5 mg. of digoxin; in the last two columns are plotted the measurements two and one-half and 16 months after recovery from right ventricular failure.

For discussion see text.

enough to cause an increase in venous pressures in the presence of a normally functioning right ventricle.

The entire chain of events which lead such cases to right ventricular failure can now be outlined:[25] Under the combined assaults of polycythemia and of an increased blood volume, and of relatively high cardiac output, all initiated by anoxia, all promoting eventually pulmonary hypertension, and all persisting for years in patients still capable of some physical activity,

hypertrophy and dilatation of the right ventricle develop. The factor precipitating right ventricular failure most frequently resides in a particularly severe bout of arterial hypoxia, on the occasion of a bronchial or pulmonary infection; this stimulates further the formation of large numbers of hypochromic red cells; the blood volume, already elevated, increases rapidly and so does increase the cardiac output. When the optimal stretch of the myo-

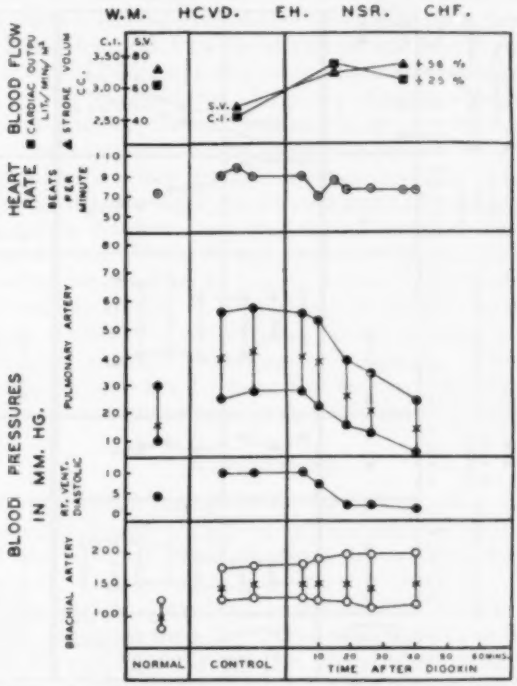

FIG. 4. Hemodynamic measurements in a case of hypertensive cardiovascular failure with combined left and right ventricular failure and a mild degree of hypervolemia.

In the second and third vertical columns are plotted the measurements before and after intravenous injection of 1.5 mg. of digoxin.

For discussion see text.

cardial fibers is exceeded the cardiac output falls from its previous level. The paradox of a high cardiac output in failure, observed in this as in other similar patients, is therefore explained by the state of the circulation just preceding the failure of the heart.

When right and left ventricular failure coexist in the absence of severe hypervolemia, one can predict the hemodynamic pattern to be found and the response to improved ventricular function following digitalization. Such

a situation is illustrated in the next case, that of a man with hypertensive cardiovascular disease in congestive failure. In figure 4 it can be seen that (*a*) pulmonary hypertension is present, presumably reflecting, as will be demonstrated later, an elevation of the left heart filling pressure; (*b*) right ventricular filling pressure, measured directly, is also elevated, and

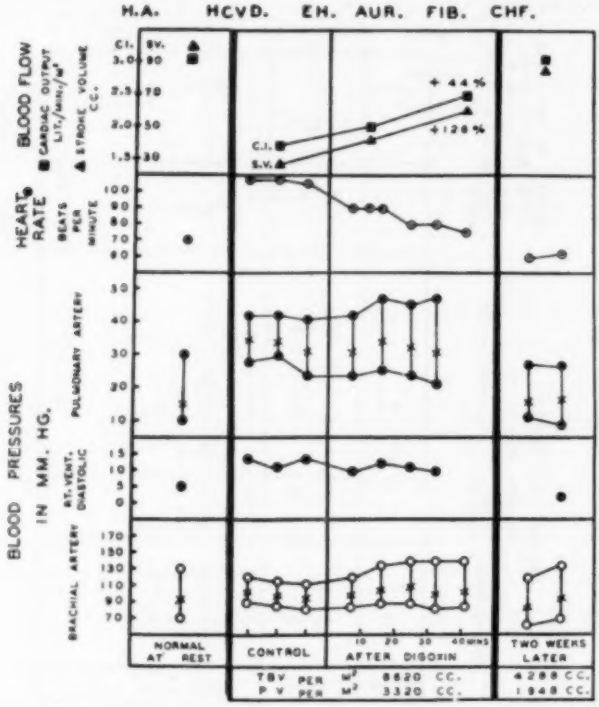

FIG. 5. Hemodynamic measurements in a case of hypertensive cardiovascular disease with combined left and right ventricular failure and considerable degree of hypervolemia.

In the second and third vertical columns are plotted the measurements before and after an intravenous injection of 1.5 mg. of digoxin; in the fourth vertical column are plotted the measurements after recovery from failure.

For discussion see text.

(*c*) the cardiac output is low. Digitalization evoked a rapid response characterized by (*a*) a return to normal of all pressures in the right heart and pulmonary artery; (*b*) an increase in cardiac output and stroke volume, and (*c*) an increase in systemic blood pressures, notably the pulse pressure. The following chain of events leading to failure can thus be reconstructed: It seems likely that the left ventricle failed first, not only because of the nature

of the disease, but also because pulmonary hypertension implies an overloading of the pulmonary circulation caused by ventricular dynamic imbalance in favor of the right ventricle. The exact cause of the later failure of the right ventricle remains obscure, but is not related to venous plethora.

The last case, in contrast, illustrates well the importance of hypervolemia in modifying the hemodynamic pattern of congestive failure during acute digitalization. As seen in figure 5, the hemodynamic measurements before intravenous digoxin therapy were almost identical to those seen in the previous case. However, the total blood volume was nearly twice as large, and therefore all the component parts of the circulation were probably nearing their limits of distensibility. Following digoxin administration, the rise in cardiac output was the most striking change. It was associated with an increase in pulse pressure in both the pulmonary and the systemic arteries. The pulmonary artery diastolic pressure and the right ventricular diastolic pressure fell only slightly and less dramatically than in the previous case. It is obvious that better emptying of both ventricles occurred. Why, then, did not the systolic and diastolic pressures in the pulmonary artery and *right* ventricular end diastolic pressure return rapidly to normal? The explanation lies, presumably, in the presence of the very large total blood volume, which prevented effective redistribution of blood, since all component parts of the circulation were near their capacity. Two weeks later, however, when the total blood volume had been considerably reduced, the pulmonary artery and right ventricular pressures had returned to normal.

Conclusions

1. The hemodynamic concept of cardiac failure which has been presented stresses that the initial cause of failure resides within the heart, and implies that each ventricle is physiologically autonomous, despite common muscle bands.

2. The fall in cardiac output from its previous level, and the rise in filling pressure of the failing ventricle, are the essential features of failure.

3. These changes are the expression and outcome of a derangement in the intimate mechanism of contraction of the myocardial fibers which, elongated beyond a critical point, liberate during systole less energy than was stored during the preceding diastole.

4. The level at which this critical point is reached depends upon the respective importance of myocardial alterations and/or of a progressive increase in venous load.

5. Further embarrassment of the failing ventricle is caused by temporary inequalities of both ventricular outputs and readjustments in blood distribution throughout the entire circulation until a new equilibrium is reached.

6. These readjustments are controlled by the importance of the initial dynamic imbalance between both ventricles and the potential margin of distensibility of the component parts of the circulation, particularly of the

systemic veins and of the pulmonary arterial system. Obviously the latter factor, i.e., potential range of distensibility, varies with the degree of volemia.

7. The heart in failure usually has a lower than normal output, but a low output in cardiacs is not necessarily failure. Under conditions of venous plethora, the output may be large, failure being then demonstrated if, with the same load, the cardiac output increases after improvement of the myocardial contractile mechanism.

I am aware that tissue metabolic changes and hormonal disturbances due to ischemia and local anoxia and their rôle in increasing the circulatory load, have not been discussed, although they eventually play an important rôle in the complex picture of cardiac failure as observed clinically. My aim has been to focus attention on the heart, and on the readjustments that take place in blood flow, blood pressures and blood volume in different parts of the circulation when it fails. In his quest for a concept, the investigator interested in hemodynamic problems may be partial to, and possibly victim of, his tools.

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CONGENITAL HEART DISEASE: A CLINICAL AND PHYSIOLOGIC CORRELATION*

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The importance of accurate diagnosis of congenital heart disease has led to the development and refinement of a series of technics and diagnostic procedures such as catheterization of the heart and angiocardiography.[1, 2, 3] Although these procedures are of great diagnostic value in the recognition of the individual malformation, they should serve another equally important purpose, the promotion of a better understanding of the clinical and radiologic manifestations of these malformations. A physician confronted with the complexities of congenital heart disease can be greatly aided by a thorough knowledge of the changes in vascular dynamics, which influence the electrocardiographic and clinical manifestations. The purpose of the present paper is to correlate the physiologic and clinical findings of the more common congenital malformations of the heart. This, it is hoped, will furnish the physician with a rational guide to the stepwise diagnosis of congenital malformations of the heart.

The technics used in this study have been previously described in the literature.[1, 2, 4, 5, 6] They consisted primarily of catheterization of the heart and fluoroscopy. A thorough history and physical examination preceded these special tests.

Previous classifications of congenital heart disease have been based either on purely clinical or purely physiologic findings.[4, 1] With the exception of Maud Abbott's classification,[7] however, they are of little practical value in the diagnosis of the individual malformation. Maud Abbott's division, which is based on the presence or absence of cyanosis alone, was introduced before the general use of fluoroscopy and before the advent of catheterization, and therefore does not represent a broad picture of congenital heart disease. An attempt has therefore been made in this report to introduce a classification of congenital heart lesions based on both clinical and physiologic findings. This, as mentioned above, is intended primarily as a guide in a stepwise diagnostic approach to these malformations.

As may be seen from tables 1 and 2, congenital malformations of the heart are divided into a cyanotic and a noncyanotic group, because the most conspicuous sign in congenital heart disease is either the presence or absence

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of cyanosis.[7] Excluding the possibility of pulmonary disease as cause of arterial oxygen unsaturation,[8] cyanosis in congenital heart disease is usually the result of an intracardiac venoarterial (right-to-left) shunt.[1] Consequently, the absence of cyanosis in a patient with congenital heart disease usually denotes the absence of a right-to-left shunt.

As may be seen from tables 1 and 2, both the cyanotic and the noncyanotic groups are subdivided according to their hemodynamic pattern. This serves the purpose of relating the malformations to the underlying basic circulatory disturbance and of presenting a physiologic basis for the radiologic manifestations of the disease. This is illustrated in tables 3 and

TABLE I

Classification of Congenital Heart Disease, Cyanotic Group

A. Pulmonary flow less than systemic flow and pulmonary artery pressure usually decreased.
B. Pulmonary flow greater than systemic flow and pulmonary artery pressure normal or increased.
C. Pulmonary flow equals systemic flow at rest and after exercise. *None.*

4, in which the principal fluoroscopic and electrocardiographic features are correlated with pulmonary artery flow and pressure.

Roentgenographic examination constitutes the most important part of the clinical examination in congenital heart disease.[4, 5, 6] The roentgenographic findings, however, remain without meaning unless the physiologic basis of the malformation is understood. An attempt to correlate roentgenographic and physiologic findings has been made by Peck and Wilson, who divided patients with congenital malformations of the heart into those with absent and those with normal or full pulmonary artery segment.[5] However, as Neuhauser[6] and Healey et al.[9] have stated, an effort should be made to

TABLE II

Classification of Congenital Heart Disease, Noncyanotic Group

A. Pulmonary flow less than systemic flow. Pulmonary artery pressure usually decreased. *None.*
B. Pulmonary flow greater than systemic flow and pulmonary artery pressure normal or increased.
C. Pulmonary flow equals systemic flow at rest and after exercise.

classify the extent of pulmonary blood flow by observation of the pulmonary vascular markings. The classification suggested in this communication attempts to correlate the various roentgenographic features with the basic physiologic disturbance. For instance, in most of the malformations belonging to Group I (pulmonary artery flow less than systemic flow, and pulmonary artery pressure usually decreased), the pulmonary artery segment is usually concave, there is a diminution in the size of the intrapulmonary vessels, and the lung fields are clear (table 3). However, there are some differences in the over-all size and shape of the heart in this group. For example, in the tetralogy of Fallot the heart tends to be small, while in

pseudotruncus arteriosus it is enlarged and more nearly boot-shaped. Wittenborg and associates have described three general categories of tricuspid atresia as based on the roentgenographic appearance of the heart.[10] In transposition of the great vessels with pulmonic stenosis, roentgenographic evidence of diminished pulmonary blood flow is present, the lung fields are clear and hilar pulsations are absent. However, the heart is generally enlarged and the aortic knob is not visible.

TABLE III

Classification of Congenital Heart Disease, Cyanotic Group. Correlation of Physiologic, Radiologic and Electrocardiographic Findings

Diagnosis	Fluoroscopic Findings				Electrical Preponderance
	Lung Fields	Size and Shape of Heart	Pulmonary Window	Pulmonary Segment	
Pulmonary Flow Less Than Systemic Flow—Pulmonary Artery Pressure Usually Decreased					
Tetralogy of Fallot	Clear	Elevated apex not enlarged, "coeur en sabot"	Clear	Concave	Right
Pseudotruncus	Clear	Enlarged and boot shaped	Clear	Concave	Right
Tricuspid Atresia	Clear	Concavity of lower right border in P.A. projection, "coeur en sabot"	Clear	Concave	Left
Transposition of the Great Vessels with Pulmonary Stenosis	Clear	Enlarged, narrow mediastinal shadow in A.P. and lateral positions	Hazy	Concave	Combined heart strain
Ebstein's Disease with Patent Foramen Ovale	Clear	Enlarged	Hazy	Convex	Right or left with bundle branch block
Pulmonary Arterio-Venous Fistula	Round Opacities	Enlarged or normal	Hazy	Convex	Right
Patent Foramen Ovale or Auricular Septal Defect with Pulmonary Stenosis	Clear	Slightly enlarged	Hazy	Convex	Right
Pulmonary Flow Greater Than Systemic Flow and/or Pulmonary Artery Pressure Normal or Increased					
Eisenmenger's	Vascular	Enlarged	Hazy	Convex	Right
Complete Transposition	Vascular	Enlarged, narrow mediastinal shadow in A.P., widening in lateral view, absence of aortic knob	Hazy		Right
Patent Ductus Arteriosus with Reversed Flow	Vascular	Enlarged	Hazy	Convex	Right
Truncus Arteriosus	Vascular	Enlarged and boot shaped	Clear	Concave	Left or right

In contrast, in patients with and without cyanosis in whom the pulmonary flow is greater than the systemic flow and the pulmonary artery pressure is either normal or increased (Group I B, II B, tables 1 to 4), the pulmonary artery segment and the vascular markings in the lung fields are usually prominent. This is the case in Eisenmenger's disease, in complete and partial transposition of the great vessels, in truncus arteriosus, patent ductus arteriosus, and in patients with auricular and ventricular septal defect, provided the left-to-right shunt is great. Further differentiation within these groups is greatly aided by differences in outline of the cardiac silhou-

ette. For example, in transposition of the great vessels the heart is usually enlarged and the mediastinal shadow in the frontal projection is narrow, with widening of this shadow in the left anterior oblique position.[4, 11] In Eisenmenger's disease, or in transposition of the aorta with overriding of the pulmonary artery, the heart is usually normal in size or only slightly enlarged.[4, 12]

In patients with isolated pulmonic stenosis (Group II C, tables 2 and 4), cyanosis is absent because the systemic and pulmonary flows are equal at rest and exercise. Because of the diminution in pulmonary artery flow and pressure, the lung fields appear clear and pulsations of the pulmonary vessels are minimal (table 4). It is of importance, however, that in this malforma-

TABLE IV

Classification of Congenital Heart Disease, Noncyanotic Group. Correlation of Physiologic, Radiologic and Electrocardiographic Findings

Diagnosis	Fluoroscopic Findings				Electrical Preponderance
	Lung Fields	Size and Shape of Heart	Pulmonary Window	Pulmonary Segment	
Pulmonary Flow Greater Than Systemic Flow and/or Pulmonary Artery Pressure Normal or Increased					
Isolated Septal Defect, Auricular					
Uncomplicated	Vascular	Enlarged	Hazy	Convex	Right
Lutembacher's	Vascular	Enlarged	Hazy	Very prominent	Right
Ventricular Septal Defect	Vascular	Usually enlarged	Hazy	Convex Convex	Left or right
Patent Ductus Arteriosus	Vascular	Enlarged	Hazy	Convex	Normal or left
Aortic Septal Defect	Vascular	Enlarged	Hazy		Normal or left
Anomalous Venous Return with Pulmonary Vein Emptying into Vena Cava or Right Auricle	Vascular	Enlarged	Hazy	Convex	Right
Pulmonary Flow Equals Systemic Flow at Rest and After Exercise					
Pure Pulmonic Stenosis	Clear	Enlarged	Hazy	Prominent	Right

tion the pulmonary artery segment is usually prominent.[13] This is probably the result of the Venturi principle, which states that if a stream bed gradually widens after a constriction the lateral pressure in the distal, wider tube is higher than in the constricted portion. This poststenotic increase in lateral pressure is the result of a reconversion of velocity energy to pressure energy which occurs as the stream bed widens.[14]

In addition to fluoroscopy, electrocardiography constitutes a part of the routine examination of patients with congenital heart disease. Since most of the patients suffering from congenital heart disease are children, a knowledge of the normal electrocardiographic pattern found in the younger age group is important. Various articles dealing with electrocardiography in

children have been published. Krumbhaar and Jenks in 1937 reported on electrocardiograms in children.[15] They mentioned particularly the frequency of right axis deviation. Similar findings were published by Burnett and Taylor,[16] who found also that the incidence of right axis deviation decreases after the fourth month, and by Hafkesbring et al.[17] and Ashman.[18] Ziegler in his comprehensive review on electrocardiography in children states that no satisfactory interpretation has been given for the characteristic form of the ventricular deflections in the standard leads of infants and children.[19] Studies of precordial leads of infants and small children are characterized by the presence of large R waves in leads from the right side of the precordium, and by the frequent occurrence of T wave inversion in leads from the right and midportion and even the left side of the precordium. The latter finding has been explained by rotation of the heart on its longitudinal axis (the right ventricle constituting most of the anterior surface of the heart), or by relative enlargement of the right ventricle. This would explain the presence of inverted T waves in leads in which the initial ventricular deflections are upright and of right ventricular origin. However, it is possible, according to Ziegler, that the precordial T wave pattern represents a single vector, dominated by the potential variations of either the right or the left ventricle.[19] The evaluation of the "axis" in infants and children appears equally difficult. Ziegler states that neither the position of the heart in the thorax nor the presence of right ventricular enlargement can be determined in infancy from the extremity leads alone (bipolar or unipolar), but that the determination requires knowledge derived from multiple unipolar precordial leads.[19] Despite these difficulties, it is certainly correct that the electrocardiogram may show characteristics in congenital heart disease which may be of diagnostic help. For instance, in tricuspid atresia there are usually left axis deviation and left ventricular preponderance.[4]

The impact of hemodynamic factors on electrocardiographic patterns has been stressed by a series of investigators. Cosby has shown that in congenital heart disease an abnormal electrocardiogram is directly related to the presence or absence of right ventricular hypertrophy.[20] It is abnormal and of diagnostic value whenever selective right ventricular hypertrophy is present. It is rarely abnormal when the work of both ventricles is increased to the same extent. Watts and associates found that the electrocardiographic pattern of right ventricular hypertrophy appeared only when right ventricular work and pressure were at least doubled.[21] Sokolow and his associates believe that the electrocardiogram is of high diagnostic accuracy in congenital heart disease.[21a]

Paul et al., from a review of the literature and from personal experience, found right ventricular preponderance in patients with isolated auricular septal defects or with Lutembacher's disease.[22] In patients with uncomplicated ventricular septal defect, the electrocardiogram may be normal or there may be right or left axis deviation.[22, 23] In Eisenmenger's disease,

right ventricular hypertrophy was the rule.[22] In tricuspid atresia, left axis is usually present.[6, 22] In isolated pulmonic stenosis, Paul and co-workers found normal axis in one case, vertical to mild right axis deviation in four cases, and a high degree of right axis deviation in three others. The precordial leads were characteristic of right ventricular hypertrophy in six out of eight patients. In pulmonic stenosis with auricular septal defect the P waves appeared peaked and the electrical axis was directed to the right.[22] The precordial leads were characteristic of right ventricular hypertrophy. In the tetralogy of Fallot there was right axis deviation and the precordial leads showed right ventricular preponderance. In transposition of the great vessels, right ventricular preponderance was the rule.

The electrocardiogram is usually normal in patients with uncomplicated patent ductus arteriosus, an abnormal electrocardiogram suggesting other cardiac malformations.[24] A prolongation of the PR interval as well as right axis deviation suggests an auricular septal defect.[24] However, it has been stated repeatedly that right axis deviation occurs more frequently in patent ductus arteriosus than had been suspected.[22] In many of these instances evidence of right ventricular preponderance is lacking, and the right axis is the result of a vertical heart pattern.

To illustrate the diagnostic value of this classification, the clinical and physiologic findings in three patients suffering from the more common forms of congenital heart disease will be discussed at this point.

Case Reports

Case 1. A 10 year old white child had a normal birth and development. During the fourth year she experienced attacks of sudden syncope lasting three to four minutes. During these spells the child was intensely cyanotic. After her fourth year, cyanosis persisted and minimal exertion produced dyspnea. When tired, she often assumed the squatting position. On occasions she experienced nocturnal dyspnea. There was no history of hemoptysis or nosebleeds.

Physical examination revealed a poorly nourished, well developed cyanotic child with clubbing of the fingers and toes. Heart examination revealed a sinus arrhythmia and a grade IV systolic murmur, loudest in the left third intercostal space. A thrill accompanied the murmur. The pulmonary second sound was not accentuated. Fluoroscopy in the anteroposterior position revealed a slightly enlarged cardiac silhouette with a concave pulmonary artery segment (figure 1). The aorta descended on the left and the lung fields appeared clear, but no pulmonary arteries were visible. In the left anterior oblique position the pulmonary window was clear. The electrocardiogram showed right ventricular hypertrophy. The clinical diagnosis was tetralogy of Fallot.

Comment: The presence of cyanosis indicated that the patient suffered from a malformation belonging in Group I, subgroup A or B (table 1). The findings of a concavity in the region of the pulmonary artery segment and the diminution of vascular markings in the lung fields indicated a reduction in the pulmonary blood flow and/or pulmonary artery pressure (table 3). The presence of a tricuspid stenosis could be excluded because of the presence of right ventricular preponderance.

Physiologic Findings: Findings obtained on catheterization demonstrated a gradient in oxygen content between blood from the superior vena cava and the right auricle, indicating the presence of an auricular defect (figure 2). Since the aorta was intubated from the right ventricle, a dextro position of the aorta was also present. The pressure in the right ventricle was 118/10 mm. Hg, that in the pulmonary artery, 16/11 mm. Hg, demonstrating

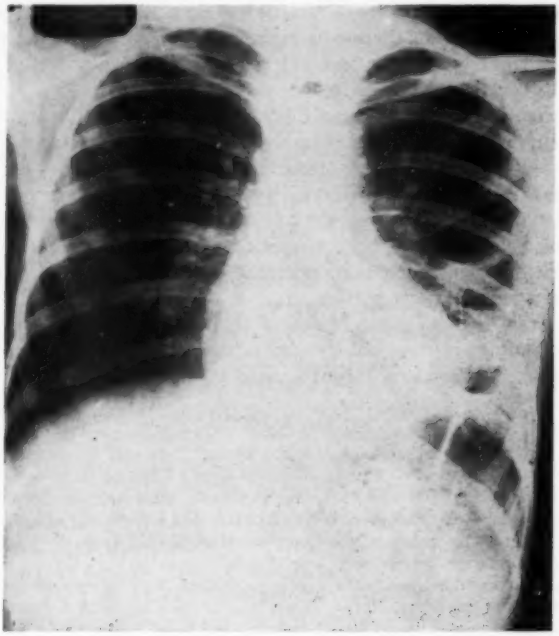

FIG. 1. X-ray of case 1 (tetralogy of Fallot with auricular septal defect). There is slight enlargement of the cardiac silhouette, with a concave pulmonary artery segment.

pulmonic stenosis. The arterial oxygen saturation was 72.5 per cent. The over-all intracardiac shunt was 2600 c.c., directed from right to left. A diagnosis of tetralogy of Fallot with interauricular septal defect was made.

Case 2. A 30 year old white male developed cyanosis during the fifth year of life. Development was normal. Exertional dyspnea was noticed during childhood but the patient never assumed the squatting position. He was able to work in a limited capacity and was free of complaints except palpitation. There was no history of hemoptysis, epistaxis or chest pain.

Physical examination revealed moderate generalized cyanosis and definite clubbing of fingers and toes. Blood pressure in the arm was 120/80 mm. of Hg; the heart rate was regular (80/min.). Prominent pulsations were present over the precordium,

and the apical impulse was localized in the fifth intercostal space at the anterior axillary line. There was an area of percussion dullness 1 cm. to the left of the sternum in the third intercostal space. A grade IV, harsh systolic murmur, accompanied by a thrill, was heard in the left third and fourth intercostal spaces. The murmur radiated to the left shoulder area and was heard with less intensity at the apex. A short, grade I diastolic murmur was present in the left third interspace. The pulmonic second sound was loud.

On fluoroscopy the heart appeared slightly enlarged in the anteroposterior position (figure 3). The pulmonary artery segment was prominent and there was a definite increase in hilar density, with "hilar dance." The electrocardiogram showed right axis deviation with evidence of right ventricular enlargement.

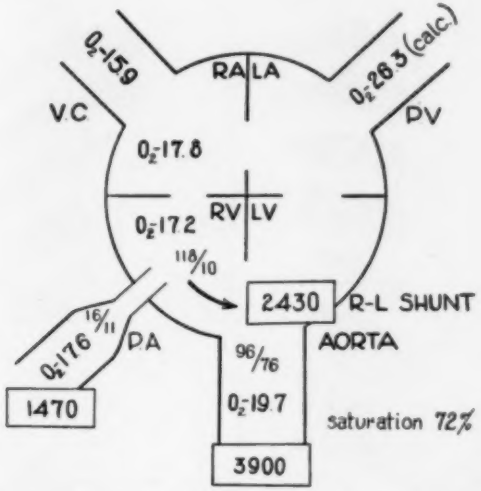

FIG. 2. Diagram of the physiologic findings obtained in case 1. There is a gradient in oxygen content between blood from the superior vena cava and the right auricle, indicating the presence of an auricular defect. The aorta overrides both ventricles. There is a gradient in the systolic pressure from right ventricle to pulmonary artery, indicating the presence of pulmonic stenosis. The over-all shunt is from right to left.

Comment: The presence of cyanosis indicated that the patient had a malformation which belonged in Group I, subgroup A or B (table 1). The radiologic observations of a prominence in the region of the pulmonary artery segment and the increase in the vascular markings in the lung fields suggested a malformation belonging to Group B (pulmonary blood flow greater than the systemic flow and/or pulmonary artery pressure increased, tables 1 and 3). As the heart was not greatly enlarged and the cyanosis was of equal intensity in the lower and upper extremities, transposition of the great vessels and patent ductus arteriosus with reversed flow could be excluded. A clinical diagnosis of Eisenmenger's disease was therefore made.

Physiologic Findings: The findings obtained on catheterization are illustrated in figure 4. It may be seen that there was a gradient in oxygen content from right auricular to right ventricular blood, suggesting the presence of a ventricular septal defect. The systolic pressures in the right ventricle and the pulmonary artery were approximately equal and markedly elevated. The intracardiac over-all shunt was 300 c.c., directed from right

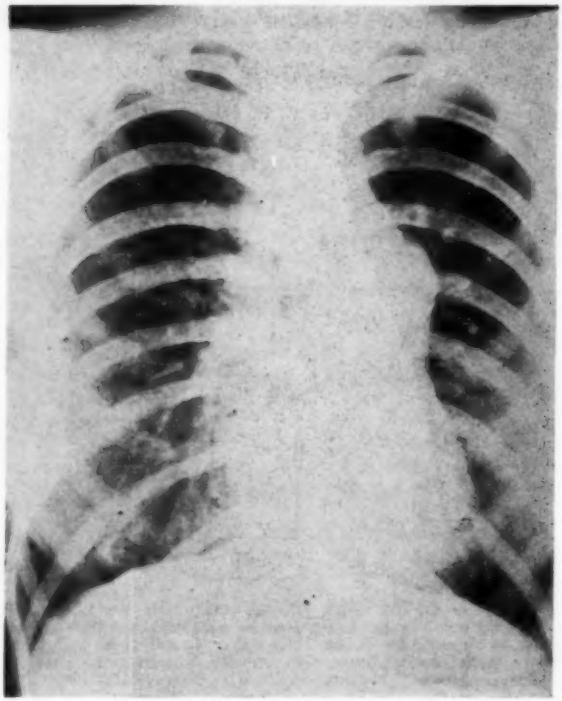

FIG. 3. X-ray of case 2 (Eisenmenger's disease). The pulmonary artery segment is prominent, the lung fields are vascular.

to left. The total right-to-left shunt was 880 c.c. and the total left-to-right shunt 580 c.c. The peripheral arterial oxygen saturation was 88 per cent. These findings confirmed the clinical impression of Eisenmenger's disease.

Case 3. This seven year old white male was apparently normal at birth, and development proceeded without retardation. At 20 months a physician discovered a heart murmur. Within recent years dyspnea on extreme exertion had been noted.

Physical examination disclosed no cyanosis or clubbing. The positive findings were limited to the heart. The apical impulse was localized in the fourth intercostal

space at the midclavicular line. A systolic thrill was palpable over the entire precordium but was maximal in the second left intercostal space. A grade IV, harsh systolic murmur, maximal to the left of the sternum in the second intercostal space, was present over the precordium. P_2 was not accentuated. The blood pressure in the left arm was 104/55 mm. of Hg. A systolic thrill and murmur were present over both femoral arteries.

Fluoroscopy revealed some enlargement of the cardiac silhouette in the anteroposterior view (figure 5). The pulmonary artery segment was prominent but the lung fields were not vascular and no pulsations were visible. In the left anterior oblique position the pulmonary window was hazy. The electrocardiogram showed right axis deviation without right ventricular strain.

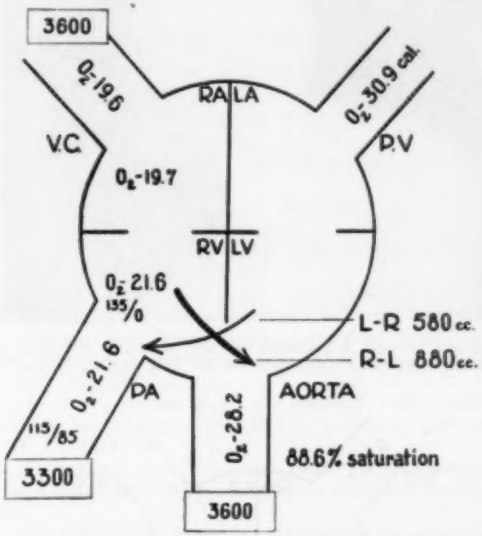

FIG. 4. Circulatory diagram of case 2. There is a gradient in oxygen content from right auricular to right ventricular blood, indicating a ventricular septal defect. The systolic pressures in the right ventricle and pulmonary artery are approximately equal and elevated. There is a right-to-left and a left-to-right shunt.

Comment: The absence of cyanosis indicated that the patient had a cardiac malformation which belonged in subgroup B or C (table 2). The radiologic observation of decreased vascular markings suggested a malformation of Group C (pulmonary flow equals systemic flow at rest and after exercise, table 2). The presence of a dilated pulmonary artery segment and of diminished vascular markings made the presence of isolated pulmonic stenosis likely (table 4).

Physiologic Findings: The findings obtained on catheterization are illustrated in figure 6. The oxygen contents of blood withdrawn from the superior vena cava, the right auricle, the right ventricle and the pulmonary

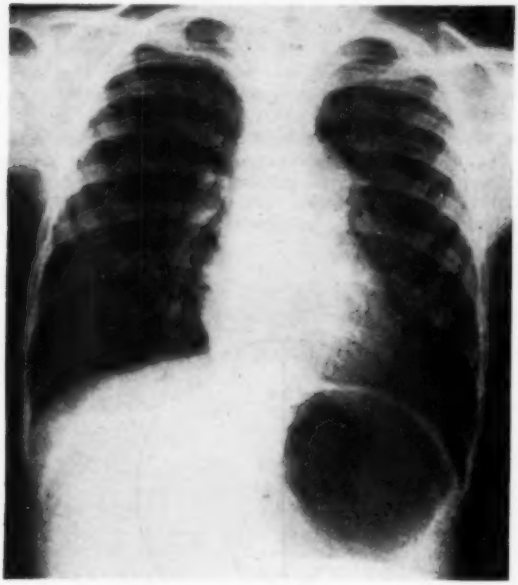

FIG. 5. X-ray findings on case 3 (isolated valvular pulmonic stenosis). The pulmonary artery segment is prominent but the lung fields are clear.

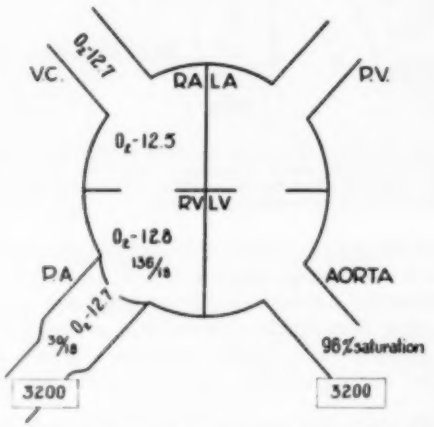

FIG. 6. Circulatory diagram on case 3. The oxygen contents of blood from the superior vena cava, right auricle, right ventricle and pulmonary artery are equal. The arterial blood is fully saturated. Consequently, an intracardiac shunt is absent. There is a large gradient between right ventricular and pulmonary artery pressure, indicating the presence of pulmonic stenosis.

artery were equal, demonstrating the absence of a left-to-right shunt. A right-to-left shunt was also absent, since the arterial blood was fully saturated. There was a large gradient between the right ventricular and pulmonary artery pressure (106 mm. Hg). These findings confirmed the clinical impression of isolated pulmonic stenosis.

The three examples illustrate the advantage of a stepwise, selective diagnosis based on physiologic, radiologic and clinical considerations. Although physiologic studies are not always essential for the diagnosis, a knowledge of the hemodynamics of congenital heart disease is valuable for a rational diagnostic approach.

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THE EMOTIONAL PROBLEMS OF HIGH BLOOD PRESSURE *

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The organic tradition in medicine has been responsible for a narrow (physical) view of the etiology, pathogenesis and treatment of essential hypertension. The psychosomatic approach does not neglect the physical problems involved but includes a consideration of the rôle of emotions. It emphasizes the multiple factors in etiology, pathogenesis and treatment, and attempts to evaluate the resulting composite clinical picture. Such studies indicate that emotional factors apparently are intimately related to the onset of hypertension in some patients (5 per cent), and to the production of symptoms and complications in many others (87 per cent), and that they enter into the question of treatment in nearly all patients with this disorder.

These conclusions, published in 1942,[1] were derived from a study of 93 patients with hypertension encountered in private practice; but, suspecting that there had been some selection favoring psychologic factors, we began a study in the out-patient department of Temple University Hospital more than three years ago of unselected, consecutive patients from the hypertension clinic. To the usual physical and laboratory studies were added a social history, a battery of psychologic tests, including Rorschach, thematic apperception, figure drawing and I.Q., and psychiatric interviews. Each week the material was discussed at a psychosomatic conference, attended by members of the medical and psychiatric staffs. One hundred fifty patients have been studied, and a control series of about 50 consecutive patients with asthma from the allergy clinic was studied in the same way. Although the material has not been completely analyzed, a number of observations have been made upon the emotional problems of hypertension and some of these we wish to discuss.

Our social and psychologic studies suggested a high incidence of neurotic tendencies in our hypertensive patients. This was confirmed by psychiatric interviews which indicated that hypertension occurs in all types of personality, from normal to psychotic, but that there is a great preponderance of neurotic personalities with strong compulsive trends. They may not show organized neurosis, but the character structure is neurotic and the evidence

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for personality disturbance antedates the discovery of the hypertension. We have been unable to discover any specific personality conflicts or specific personality structure that seemed related to the hypertension. While evidence of repressed hostility was commonly found, the same thing can be said regarding many other so-called psychosomatic disturbances; and we cannot say from our studies that repressed hostility is any more common in hypertensive patients, or that the nature or degree of its repression differs in hypertensive patients from those with other psychosomatic disturbances.

A common pattern in a great many of our patients was a background of an ineffectual father and a dominating mother, early insecurity, with the individual forced into premature independence, followed by lifelong frustrated dependency with an inhibition of the resulting hostility, which was sometimes completely repressed. There was a high incidence of sexual inhibition and a great deal of marital incompatibility. Their fantasies showed that they were preoccupied with death, and the dreams were of an anxiety nature. Thus we dealt with a great many passive and dependent individuals whose conflicts arose out of this background. But we were dealing with a clinic population, with many colored patients, so that this background was not unusual. It remains to be demonstrated whether it is any more common in a hypertensive population than in a nonhypertensive population from the same social setting.

To sum up, about all we can say with certainty is that a study of unselected patients in a hypertension clinic shows a high incidence of neurosis and accompanying emotional problems, but we are not able to designate a neurotic pattern that is specific for hypertension.

One aspect of the study, which is generally accepted, was the high incidence of hypertension and cardiovascular-renal disease in the family background of the hypertensive patients. Our feeling is that, given this constitutional predisposition, emotional stress which is specifically related to the character structure of the individual is a frequent precipitating factor in essential hypertension. Certainly the symptoms which lead to the discovery of the hypertension arise under such circumstances.

While the symptoms that occur in patients with hypertension respond readily to psychotherapy, the blood pressure is less amenable, and we have no evidence that the course of the hypertensive vascular disease can be influenced by psychotherapy, no matter how intensive or prolonged. This has no bearing on the question of whether emotional factors are of fundamental importance in hypertension, nor does it detract from the value of psychotherapy in dealing with this disorder. By this we mean that, whatever the nature of the stimulus initiating the hypertensive process, evidence suggests that with rare exceptions the process becomes irreversible.

Most of the previous psychologic observations on hypertension have been made on a small number of selected patients and for that reason are of limited value, but studies very similar to ours have been made and recently published by Reiser and his associates in Cincinnati.[2] Our observations are

almost identical with theirs. They studied 230 unselected patients in much the same way we did. Special attention was paid to the natural course of the disease, the rôle of emotional factors, physiologic mechanisms involved, and the response of the patients to various pharmacologic agents and therapeutic procedures. The frequency of correlations that could be established between emotionally stressful life situations and the onset, symptoms and complications in hypertensive cardiovascular disease rose progressively to 100 per cent in their most intensively studied group, suggesting that the more intensive and thorough the study, the higher the frequency of correlations that could be expected. Their data also demonstrate the high frequency with which emotionally relaxing situations—such as the doctor-patient relationship—may improve the patients. They stress the fact that the doctor-patient relationship, regardless of one's recognition of it, is an ever-present and potent therapeutic tool in the management of the disease, and for this reason any response to "specific" therapy in hypertension needs to be interpreted in the light of the influence of the doctor-patient relationship which parallels it.

As part of a comprehensive study of this disease, they investigated 12 patients who were in various stages of the transition from benign to malignant hypertension.[3] In each of these patients, examination of the relationship between the life history and the medical course of the disease revealed that the precipitation of the malignant phase could be chronologically correlated with emotionally significant life situations or events. It was felt that the data pointed toward the existence of a meaningful and understandable system of interrelated forces underlying these chronologic correlations. In the individual case, the precipitating events could be related to specific dynamic constellations in the patient's total personality. Further, these same constellations in the individual patient could be linked with the events associated with the onset of benign hypertension, fluctuations in blood pressure and exacerbations of the clinical course. They emphasized that these correlations are specific within the individual patient, but that their data did not reveal any specificity of personality structure or conflict situations for the group as a whole.

The Phobia of High Blood Pressure

High blood pressure frequently makes its appearance in a setting of emotional stress in which there is a specific relationship between the emotionally disturbing event and the personality structure of the individual. It appears in a situation of emotional conflict or, at least, symptoms appear which are attributed to the hypertension. Whether the hypertension is an evidence of the personality decompensation is difficult to say from our evidence, although infrequently this has seemed to be the case. In other words, so often we cannot tell whether the high blood pressure did not precede the symptoms which led to its discovery and are then attributed to it. Never-

theless, as soon as the blood pressure elevation is discovered and the patient informed, the "blood pressure phobia" appears. It is so easy for a practicing physician to slap a blood pressure cuff on the arm of a patient and say, "It's your blood pressure"; it is so difficult to spend time with a patient trying to find out something about the emotional life. Once the diagnosis of "high blood pressure" has been established, attention is concentrated on the effort to "bring the blood pressure down." The patient demands to know the blood pressure figures; on each visit to the physician he waits with anxious concern to hear the latest reading, and frequently he has ideas of "stroke," "heart failure" or "Bright's disease" in the back of his mind.

It is hardly necessary to detail what has been done to this poor fellow in an effort to "bring his blood pressure down." There was a day when protein, and red meat especially, was looked upon with particular dread. This was followed by a period in which the diet was rendered even more unpalatable by the withdrawal of salt. After a lapse of 25 years this salt-free era has been reëstablished, only rice has been added. The palatability has not been enhanced by this addition. Then we must not forget the period when an avid search was made for "focal infections," and teeth and tonsils were sacrificed at a prodigious rate. Nor was the colon neglected in this search for "toxins," and "colonic irrigations" were very popular for a time. The patient still is often told to stop work and exercise, and is denied alcohol and tobacco as well as coffee and tea. Having been reduced to a vegetative existence, the unfortunate hypertensive has been threatened with mutilation at the hands of the neurosurgeon who, during the last decade, has removed more and more of his sympathetic nervous system, including his adrenal glands. All of this has gone on with hardly the slightest attention to the personality of the hypertensive individual, and, of course, this concentration on "bringing the blood pressure down" has only added to the phobia of high blood pressure, with all of its attendant secondary ills.

The phobia becomes the predominant part of the clinical picture, and the symptoms are only an exaggeration of the premorbid personality trends. In benign hypertension, often the best treatment is simply an effort to deal with this "blood pressure phobia" by reassurance, less preoccupation with blood pressure figures and weird diets, the advice to "carry on in spite of symptoms," and the attempt to understand the patient as a person.

The following case is an example of the setting in which high blood pressure arises and of the phobia which follows. Although the circumstances are unusual, the pattern is a common one.

Case Report

A 42 year old white woman was seen in the out-patient department with a history of headaches, palpitation and pain in the heart region which had begun 15 years before. At that time she was told that she had high blood pressure. She consulted a number of physicians, then went to the clinic of a woman's hospital, "but felt no confidence in women physicians." After trying osteopathy she came to our clinic.

She felt as though her head would "explode" and as though something were "probing" to get out—"something was running or flowing down inside the head on the left side."

The past history otherwise was negative.

The mother had been hypertensive for a few years but was now 77 and only recently had had "a light heart attack." The father had died of cirrhosis in April, 1940; he had been an alcoholic.

A sister suffered from migraine, and one brother had been turned down by the Army because he was nervous.

General physical examination showed moderate elevation of blood pressure, varying between 170/100 and 180/114 mm. of Hg, but in spite of the long history of hypertension there was remarkably little change in the cardiovascular-renal system. The heart was normal in size, urinalysis negative and the kidney function good, and there was only slight attenuation of retinal arterioles, with a mild degree of sclerosis of the peripheral branches.

The patient was reassured about her physical condition and was asked to describe in more detail the onset of her difficulties. She told us that at the time she had felt confused, and had suffered from headache and a sense of rushing or being pushed all the time, and that she had thought of a mental condition "because a cousin of her husband's had had some kind of a mental condition for many years." However, a physician told her that it was high blood pressure, and from then on she accepted that explanation of her illness.

Life History: She had gone to public school to the eighth grade and then had had various jobs until she married at 19. There was one child, a son, now 22.

Her father had been a brewer, born in Germany, an alcoholic; the mother was a good hearted, kind woman, much upset by her husband's drinking. The patient had been afraid of her father, who was very strict. She had had to give up school at 14, just before finishing the eighth grade, because the father was sick and out of work; afterwards, the father worked now and then but "drank most of the wages."

She had known her husband for several years before marriage. For the first five years they lived with her parents. He worked as a bank clerk, and is still with the same bank.

Fifteen years ago (at the time her illness began), she was very proud of the new home they had recently built, and as they were about to leave on a vacation she cleaned the house thoroughly, her usual practice. On her return she was amazed to find some cockroaches in the kitchen. She put roach powder about the house and then became upset on finding all the dead roaches. This continued all through the summer; she kept putting roach powder around, finding dead roaches and became "obsessed and frantic," so that she couldn't sleep or eat, and lost weight. She called in an exterminator, who "laughed at her"—he regarded the problem as so insignificant. But she would get up in the middle of the night and crawl around on the floor to look for roaches. She was so ashamed of her obsession that she would sometimes send her husband to the movies so she could look for roaches without his knowledge. She dreamed of them. The trouble continued for five years, the patient says, but she admits that when summer comes around now she is still uneasy and looks for roaches.

It was at this time that she went to her physician because of a "confusion in her head" and a fear that something was going wrong with her mind. It was then her doctor told her that high blood pressure was the cause of her trouble.

She had always been an excessively clean, meticulous person about herself and the house. Now she says that this has lessened somewhat, that she was silly, and that she will never be that way again.

She is a very neat, attractive, gray haired woman in her early forties, gentle and soft voiced; she speaks in terms of high praise of her mother and husband. She

has had a great disappointment in her son, who refused an education. She had wanted him to be a physician "from the day that he was born."

The patient says that nothing else in her life ever upset her as much as the roaches. She had never discussed it before because she was afraid of being thought silly. She says that she was always a perfectionist, and that the roaches represented an imperfection. She felt that having them "was close to being a sin," so that we get some insight into her obsession with dirt.

She was presented in psychosomatic conference and later was disturbed by thoughts—"Did I do right—did I answer correctly?" She felt very guilty when she was questioned about her religion; she was ashamed to admit that she did not go to church.

She is still fearful that something will happen to her mind and that, if it does, it will also affect her boy's mind. When she was given a Rorschach test it increased her doubts about her sanity, and for a week afterwards, until she was once more reassured, she had considerable headache and "confusion' 'in her head. The Rorschach test showed her compulsive trends, indications of sexual difficulties and some paranoid tendencies.

Although she improved remarkably after her interviews, the blood pressure was still elevated.

Follow-up: One year later the patient continued free of symptoms. Her son had married and had entered military service, and she had resigned herself to the situation as "other mothers have to do." She confessed that she still gets a little uneasy when spring approaches and she thinks about roaches. The blood pressure continues to be moderately elevated.

Summary: An instance of hypertension arising in the setting of an emotional illness, compulsive in nature. Apparently the blood pressure elevation had not been constant, because so few changes had occurred in the cardiovascular system. Certainly the blood pressure elevation has nothing to do with her symptoms now, and probably did not have in the beginning of her illness. It is also likely that, with so little impairment of the cardiovascular-renal system, the blood pressure is not even a threat to a normal span of years.

And now let us refer to some of the other important problems that are apt to arise especially after the discovery of high blood pressure.

Vertigo

Patients frequently refer to the symptom of vertigo as dizziness and giddiness. Differentiating syncope, which does not imply a disturbance of equilibrium, and true Ménière's syndrome, one often finds that the symptom of vertigo bears a definite relation to an anxiety state. Frequently in association with ringing in the ears and sometimes with numbness and tingling of the extremities, it is the result of psychic stress. When vertigo occurs in association with hypertension, the vascular disease is often held to be responsible. However, it is well to bear in mind that, like organ language elsewhere, vertigo (unsteadiness) is frequently the symbolic representation of insecurity and indecision, and this is just as true when it occurs in association with hypertension.

A woman of 55 with a moderate elevation of blood pressure and pronounced symptoms of cardiac neurosis recently suffered an attack of severe vertigo. She was thoroughly studied at the hospital and no evidence of organic disease other than moderate elevation of blood pressure was found. The study included a complete neurologic survey.

As one of us was leaving her room after the last interview, a casual comment seemed to have more bearing on the vertigo than all of the examinations just completed. In the course of the conversation, she said, "You have much to live for (meaning the profession of medicine), while I have nothing."

She had always aspired to a career in medicine, encouraged by a dominating mother who directed her own ambitions to the daughter. Instead, she married a man whom she idealized as a perfect person, "not primarily interested in woman as a sexual object," only to find that he made constant sexual demands. She never attained sexual gratification, but had five children in rapid succession. She devoted herself to her children (now grown). Following the death of her mother from heart disease, she developed a mild depressive reaction from which she had not recovered. The discovery of the hypertension permitted her to focus her anxiety upon her heart and the fear of death from a "stroke."

She was referred to a psychiatrist and, with psychotherapy, was able to recognize and express the hostility against her husband, but she had more difficulty with her guilt-laden wishes against her mother. It was with great difficulty that she was able to see her mother's domination and her own need for her mother's love, which had determined her pattern of submission, the development of unconscious wishes for her mother's death to relieve herself of this burden, and the ensuing guilt, which increased her own need to act the dutiful daughter. Then, from this identification, she punished herself with her mother's symptoms of heart disease, especially after anything that she considered self-indulgence or ostentation. After the "heart pain" there was a secondary depression associated with feelings of helplessness and inadequacy.

During the course of treatment her depression diminished and she was able to engage in more activities, such as a class in music appreciation, from which she derived great pleasure. The atmosphere at home improved. Then of her own accord she suggested diminishing the frequency of her visits to the psychiatrist, and immediately after this had the attack of severe vertigo that resulted in the hospital study. We thought of the symptom as representing symbolically her fear that she might not be able to maintain her balance without supportive therapy, but perhaps on a deeper level it had to do with fear of "falling" in a sexual sense.

Unconscious depreciation of femininity had colored her whole life as a disappointment that could not be fulfilled. The substitution was to have children and be a perfect mother, but, with her children grown and no longer needing care, her illness was precipitated by the death of the mother with whom she was strongly identified. When she no longer had the gratification of motherhood, pains in the chest acted as a constant reminder of her inadequacy. They meant, "I can never hope to attain the goal that mother wanted for me," and a life of leisure and self-indulgence only added to her woes.

Sympathectomy

There is no objection to the effort to lower blood pressure so long as this does not constitute the sole approach to the problem. This applies to the recent methods of dealing with hypertension by surgical means. In some patients, sympathectomy will produce a prolonged drop of the blood pressure, often, it is true, accompanied by unpleasant side effects.

Among the secondary effects of sympathectomy the disturbance in sexual function has recently been studied by Whitelaw and Smithwick.[4] From an analysis of 183 cases they find that when L_1, L_2 and L_3 are removed on both sides, significant change in sexual function can be expected in at least 63 per cent of cases. However, the vast majority of their patients with serious cardiovascular disorders, particularly those who do not plan to have any more children, do not wish to have possible changes of sexual function considered in the decision concerning exactly what ganglia should be removed. Nevertheless, they believe that it is wise to apprise the patient of the possibilities in this regard before operation and to allow him to make the decision.

That the problem is more than "organic" is illustrated by the following case.

A man of 48, first seen in March, 1947, had learned of his elevated blood pressure some three years before. He presented the clinical picture of malignant hypertension. Blood pressure figures averaged 240/160 mm. of Hg during a period of three months' observation, and eye ground findings of extensive retinitis progressed. Dorsolumbar sympathectomy T2–L2 was performed in May, 1947, and was followed by a marked lowering of blood pressure and pronounced postural hypotension. The blood pressure has remained low over a period of five years and at present averages 130/90 mm. of Hg, with no significant postural hypotension. Eye ground findings have cleared completely, leaving only slight evidence of arteriosclerosis of the retinal arterioles. However, the patient became impotent, although he does get erections and occasional ejaculations at night. One would be apt to attribute this to the operation, except that careful inquiry reveals that there was some difficulty with potency for many years before operation. This is not unusual in hypertensive subjects and represents just another phase of their emotional disturbance. In the present instance it was obvious that the high blood pressure and the impotence represented to the patient punishment for sex indulgence, and this, in turn, seemed to be due to his very strict and moralistic upbringing. Although he now regarded himself as a "changed personality," in that he no longer coveted his superior's job and was satisfied to "coast along," this resignation apparently represented a suppression of his aggression in order to feel at peace with himself.

One of the fundamental issues raised by such a case as this concerns the energy distribution in psychosomatic disorders. One must postulate that, if hypertension is truly a psychosomatic problem, then it means that the energy distribution has been influenced by repression (due to unconscious conflict), so that some of the energy that would ordinarily be utilized for work and social purposes "short-circuits," so to speak, and is deflected into the circulatory system, where it augments the hypertension. If, then, the nervous pathways that transmit this energy are severed by sympathectomy, what becomes of it? Is the organism then capable of utilizing it for useful purposes, or must it remain inhibited and exert itself in some other noxious manner—in other words, cause other mental or bodily symptoms? Is this man's impotence, tendencies for which were already present before operation, the price that he must pay for the improvement in his hypertension?

Cardiac Neurosis

Pain in the precordium, palpitation, dyspnea and fatigue are a group of symptoms frequently associated with the cardiac neurosis that occurs in patients with hypertension. Fatigue may be a prominent part of the clinical picture, in fact, the most prominent symptom, although again and again the patient speaks of pain in the heart region and only after considerable discussion is it brought out that really the most important symptom is fatigue, that it occurred first, and that only later was the pain added. One of the most common causes of fatigue is emotional conflict, which steals energy that then is not available for useful purposes.

When these symptoms are present with a normal cardiovascular system, and the general medical examination is otherwise negative, it is not as a rule difficult to assign them to their proper sphere—the emotions. When hypertension is present, however, it is almost invariably held to be the responsible factor. It is under such circumstances that psychosomatic study will frequently reveal that symptoms are out of proportion to disease, and that there is much conflict in the personality makeup. Moreover, a specific as well as a temporal relationship will be found between the onset of the symptoms and an emotionally disturbing event.

Thus, in regard to symptoms in association with hypertension, one must always question their relation to the high blood pressure itself and make an effort to understand them from the viewpoint of behavior.

When pain in the chest is associated with hypertension in a middle aged individual, and especially in the presence of physical evidence of cardiovascular disease, the problem becomes a very difficult one from the standpoint of management. It is all very well to advise a young person invalided by cardiac neurosis but with only moderate elevation of blood pressure and no evidence of cardiovascular disease "to carry on in spite of symptoms," and to encourage him to do the things that other people do. But in the presence of electrocardiographic evidence or other indications of coronary disease, one assumes a heavy responsibility in encouraging such patients to carry on; yet to caution rest on the one hand and try to give reassurance on the other is so often worse than useless. To the young physician treating such a patient, and to psychiatrists as well, it poses a very difficult problem: the sudden death that may occur in patients who have been encouraged to carry on, or who are undergoing psychotherapy, may bring the criticism of the community down upon the head of the unfortunate practitioner. And yet to play into their unconscious fears by cautioning rest and more rest leads to greater and greater degrees of invalidism. Moreover, as the patient waits for his arteries to harden the questionable benefit of the physical rest is more than offset by the physiologic burden provoked by psychic stress. The only advice that we can offer in this regard is that the patient must be evaluated as carefully as possible, both physically and psychologically, and then an effort made to advise him correctly regarding his activities. Ten-

sion of emotional origin is just as burdensome to the cardiovascular system as effort of physical origin, if not more so.

Psychoanalysis

Because of the involved emotional problems frequently presented by patients with hypertension, psychoanalysis is sometimes advised.

A young man with essential hypertension and angina pectoris was referred for analysis because of serious personality problems. It was a long and difficult analysis, but the patient made great social improvement and became a more effective personality. Nevertheless, the cardiovascular disease was uninfluenced and, indeed, showed evidence of progression.

One should approach a problem like this from the standpoint of the psychologic difficulty. It is not that the hypertension needs analysis but that the patient needs analysis. At the same time one must bear in mind the physical threat imposed by the cardiovascular disease. Will the stress of the work of analysis threaten such a patient? Has he a chance to live out enough years to make the investment in time, energy and money worthwhile? Should one ask the analyst to assume such a responsibility in the face of coronary disease and the threat of sudden death? When coronary artery disease exists in a patient with a seriously disturbed personality, I think we have to question whether to advise analysis or to be satisfied with superficial psychotherapy and reassurance.

To give further emphasis to the point that the hypertension itself is not influenced by analysis, we cite the following case of what appears to be early, mild essential hypertension.

A white man of 31 was first seen in March, 1944. He had been called before the Induction Board in October, 1940; two doctors had examined him, and he thought he heard the term "aneurysm" used in connection with his case and "hasn't been right since." He had many symptoms referred to the circulatory system, and dull headaches and depression.

Later he was rejected by the Board, he says because of hemorrhoids, and still later received occupational deferment until June, 1944. The previous summer he had contracted gonorrhea, "had been knocked out by sulfa," and then all of his old symptoms, which had been in abeyance, returned.

He had never had a serious illness, but gave a history of repeated fainting, usually in connection with hospital experiences, such as visiting a sick friend, so that he "hates hospitals."

The physical examination showed that the blood pressure was somewhat elevated, varying between 160 and 180 systolic and 95 to 120 diastolic, but was otherwise negative for evidence of organic disease. In particular, the cardiovascular-renal system seemed to be normal, so that the hypertension was thought to be of the essential variety.

The patient said that his parents had separated when he was four or five and had finally been divorced five years ago, when the patient was 26. There were six siblings, but there was nothing remarkable about the medical history other than that the mother was subject to migraine headaches.

The patient was seen about once a month (he lived in another city), and the blood pressure remained about the same but symptoms diminished. However, from

time to time he continued to have various anxiety symptoms and mild depressions, and in 1947 it was possible to refer him for analysis. The analysis continued for about two years, and the following notes were sent to us by the analyst at the end of this period.

"With the patient's permission, I am glad to send you some account of relevant factors which his psychoanalysis has brought out.

"He is the youngest child who has known all his life that his mother regards him as her favorite, but wanted him—both before his birth and ever since—to be a girl. He has been very much attached to her and has been desirous of, and very rebellious against, giving in to her wishes. Thus, he wore long hair and 'sissified' clothes until a very late age, when he finally insisted upon becoming more boylike. His three older brothers did not include him in their play or work endeavors, which led him to feel inferior, hostile and depressed. His overly religious severe father seemed forbidding to the patient, who nonetheless felt ashamed and inferior 'not to have a father like other children' when for several of his childhood years the father abandoned the family. He was relieved when at 14 his father returned. But then, as always, it was the mother who was careful, energetic, and who saved money, and it was she who seemed to the patient to be a good example.

"He had a great deal of castration anxiety which had to do with his many syncopal attacks. Thus visiting a cousin in the hospital who had been circumcised, the patient fainted, and from then on he feared and hated hospitals. As he reached his late teens, there developed a severe conflict between his fears of approaching girls sexually and his over-accentuated urges to conquest. The latter won out, and he has since had continuous Don Juan activities in which numbers of conquests were very important to him. Among them all, only four were 'special.' They were all tremendously appealing to him sexually. Each was dark haired and about five feet tall. His mother was dark haired and five feet tall.

"As the analysis proceeded he has grown steadily better able to separate the infantile hangovers from present day reality situations. After he had learned about his wish to be feminine, to give up his penis to please his mother, he began to stack this wish up against his masculine competitive longings and to assign them their correct rôles. When he had worked over the Oedipus attachments to his mother, he became less interested in promiscuity. His fears of marriage as a 'cutting down upon' his freedom gradually diminished to the point where he could accept being a father. He then legally married the girl he had been living with—a dark haired girl, five feet tall. When pregnancy occurred, he was pleased and proud; since a baby girl has been born, he is quite able to accept the father's rôle. He is a fairly considerate husband. He is able to show sympathy, affection, self sacrifice. He can be critical for cause, both at home and more realistically in business relations with men. When his mother died several months ago, he accepted it in average fashion.

"Recently we have cut down two sessions per week, and he is polishing up various details and synthesizing matters. His episodes of anxiety are not yet totally absent, but he is able to minimize them and can always find for himself what had re-animated a bit of the old castration dread. His breadth of vision has markedly widened."

He was not seen between the time he started analysis (October, 1947) and March, 1950. His physical condition was unchanged except that he had gained about 30 pounds in weight (he was very tall and had been quite thin, so that it was possible for him to carry this increased weight); but the blood pressure figures were the same, and eye ground examination showed the generalized narrowing of the arterioles that is indicative of a preorganic hypertensive change, but otherwise the cardiovascular-renal system was normal.

The patient was seen a year later and again two years later, and although he reported himself free of symptoms, making good in business, successful in marriage

and the father of a fine child, his blood pressure has continued to be elevated at the same figures as had been previously obtained.

Summary and Conclusions

The symptoms of hypertension usually arise in a social setting of emotional stress. Hence, one must always question their relation to the high blood pressure itself, and make an effort to understand them from the viewpoint of behavior. With the discovery of the hypertension the "blood pressure phobia" begins and often dominates the clinical picture; the new symptoms are only an exaggeration of the premorbid personality trends. These symptoms respond readily to psychotherapy, but we have no evidence that the course of hypertensive vascular disease can be influenced by psychotherapy, no matter how intensive or prolonged. Therefore, while hypertension in itself is not an indication for psychotherapy, the emotional problems that occur in association with hypertension are; and because they are so common, psychotherapy is indicated in the great majority of patients with hypertension. There is no reason why psychotherapy cannot be combined with medical and surgical treatment.

Hypertension occurs in all types of personalities, from normal to psychotic, but there is a great preponderance of neurotic personalities with strong compulsive trends. We have been unable to discover any specific personality conflicts or specific personality structure that seems related to the hypertension. Repressed hostility is not peculiar to hypertension, as opposed to other psychosomatic disorders.

From our observations, it would appear that the hypertensive predisposition and the personality fault are parallel disturbances, the one inherited and exhibited in the somatic sphere, the other manifesting itself in the emotional life through thoughts and feelings. When the life situation becomes sufficiently disturbing for the particular personality, the hypertension may appear as one aspect of the personality decompensation. Having appeared, it usually pursues an irrevocable course.

Our failure to deal adequately with hypertension stems in large part from our concern about "bringing the blood pressure down," and from our failure to recognize the emotional origin of most of the symptoms that are attributed to the high blood pressure.

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THE NATURAL HISTORY OF SYPHILITIC HEART DISEASE*

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THE unusually high incidence of syphilitic infection among the Negro population of Charleston, S. C., and its environs affords an excellent opportunity to study the disease in its many manifestations. Our experience has suggested to us that some of the current teaching concerning syphilitic cardiovascular disease may be on less firm ground than, for example, in rheumatic heart disease. In order to evaluate more objectively a number of features of syphilitic involvement of the cardiovascular system, the authors have reviewed a large amount of autopsy material and attempted to relate it to the clinical course of the patient before death.

The material was drawn from the records of the Department of Pathology of the Medical College of the State of South Carolina during a 22 year period from 1928 through 1949. In this period 5,505 autopsies were performed, of which 450 were stillbirths. Of the remaining 5,055, evidence of syphilitic aortitis or its complications was found in 569, or 11.3 per cent. In comparison, 81 instances of rheumatic involvement of the heart were found, an incidence of 1.6 per cent and only one-seventh the frequency of syphilitic cardiovascular disease. Aortic valve insufficiency due to syphilis was present in 163 cases, or twice the incidence (81) of all types of rheumatic lesions.

Certain local factors influenced this preponderance, but most important is the high incidence of syphilitic infection in the Negro population. Although the ratio in number of autopsies was 3,846 Negro to 1,209 white (3.2:1), the ratio in cardiovascular syphilis was 488 Negro to 26 white (18.8:1). The corrected autopsy incidence is 5.9 cases of cardiovascular syphilis in the Negro to one in the white. In reviewing the clinical histories of these subjects, it was found that in the few instances where a significant amount of treatment was given, symptomatic tertiary lesions had already appeared before it was begun. Moreover, penicillin was not used primarily as an antisyphilitic measure in any case. Hence the group as a whole may be considered as having had either no treatment or inadequate treatment, and the syphilitic process regarded as having run its course with little or no hindrance. For this reason we believe the title of this paper to be appropriate.

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Types of Cardiovascular Syphilis

Broadly speaking, of every four patients who showed cardiovascular syphilis at autopsy (total, 569), two (total, 275) had uncomplicated syphilitic aortitis and died of an intercurrent disease; one (total, 163) had aortic valve insufficiency and died of congestive heart failure, and one (total, 112) had an aneurysm and died of rupture of the aneurysm or compression of neighboring structures. The third most common complication of syphilitic aortitis, coronary ostial stenosis, was quite frequently found (total, 103) in its milder degrees, but usually did not perceptibly alter the course of the aortitis, valvulitis or aneurysm with which it coexisted.

In the clinical features to be discussed in subsequent paragraphs, note must be made that of the total of 569 cases with cardiovascular syphilis, there were 34 coroner's cases, and 21 others with inadequate clinical records, leaving 514 cases satisfactory for use in arriving at percentage figures for clinical findings.

Syphilitic Aortitis: The clinical diagnosis of syphilitic aortitis was rarely made in this series and was usually an incidental finding at autopsy. It was uniformly asymptomatic. The only helpful findings in making a clinical diagnosis were a positive blood Wassermann reaction, plus either a tambour quality of the second aortic heart sound or the radiologic evidence of a dilated ascending aorta. The frequency and tendency to remain uncomplicated have been the subject of some conjecture.[4] The latent period before the cardiovascular lesions appear clinically is highly inconstant and varies from months to as long as 50 years.[5] Of our 275 autopsied cases of uncomplicated aortitis, 9 per cent (25 cases) were in the age group 20 to 30 years, 88 per cent (242 cases) were from 30 to 70 years of age at death, and 3 per cent (8 cases) were over 70 years. Any attempt at establishing the time of a primary lesion in a significant number of these patients was impossible from the histories.

Syphilitic Aortic Insufficiency with Congestive Heart Failure: There were 120 cases suitable for analysis in which syphilitic aortic valve insufficiency was the sole or the principal reason for congestive failure, although the aortic valve was involved in 43 other cases which had to be discarded because of inadequate clinical records.

Males predominated in the ratio of 3 : 1 over females. The Wassermann reaction was unequivocally positive in 88 per cent. In no case was it negative or doubtful in the age group of 20 to 30 years.

Age: Seventeen and one-half per cent (21) of our patients died of this disease in their twenties. The majority were in middle age (30 to 60 years) at death. It is of interest that four cases survived beyond the age of 70 years; actually, their disease was not manifest clinically until this period of life.

Auricular Fibrillation: Probably it is too often overlooked that there is a measurable incidence of auricular fibrillation in syphilitic valvular disease.[2]

It was evidenced in 10 per cent of our cases by electrocardiographic or acceptable clinical evidence, and was scattered through all age groups about equally. Rheumatic heart disease was associated in one case and digitalis intoxication could not be ruled out in another, but three of the patients with auricular fibrillation were misdiagnosed clinically as rheumatic heart disease. It would be difficult to state precisely what rôle coronary sclerosis played, but it appeared to be no more prominent pathologically in these cases than in those with no arrhythmia. Ostial stenosis played no discernible rôle.

TABLE I

Number of Patients Dying in Each Decade from Congestive Heart Failure Due to Syphilitic Aortic Insufficiency

Age.....	20–29	30–39	40–49	50–59	60–69	70+
No.	21	33	27	23	12	4

Bacterial Endocarditis: This complication was present in nine of the 120 cases of heart failure. Three of these appeared to be acute. Of the six remaining subacute forms, one had associated rheumatic heart disease. Two of the cases were misdiagnosed clinically as rheumatic heart disease, but the latter was found at autopsy in only one case in whom it had not been suspected during life. Similar incidences of bacterial endocarditis as a complication of syphilitic aortic valvulitis have previously been reported.[6, 7] In all but one of our cases, the development of bacterial endocarditis appeared to precipitate the onset of congestive failure, and this is in agreement with the well known tendency of bacterial endocarditis to occur in rather well compensated hearts. Observation of valves in various stages of injury from syphilis showed some instances of hyaline degeneration overlying severe endarteritic changes within the aortic valve, followed by ulceration and fibrin deposition resulting in a form of sterile vegetation, which may well be the substratum on which bacterial endocarditis begins in this disease. We shall demonstrate later the very short period between the occurrence of syphilitic aortic valvulitis and the development of severe congestive failure and death in the majority of our cases.

We offer the theory that the rarity of the complication of bacterial endocarditis in syphilitic valvular disease depends upon the low incidence of valvular endarteritis affecting the endocardial surface to form the proper substratum; and the short time of survival of the patient thereafter, offering less opportunity for the engrafting of bacterial colonies than in rheumatic and congenital lesions.

Mural Thrombi: Antemortem thrombi were present in the hearts of one-fourth (30 cases) of this group. They were for the most part (24 cases) in the right atrium, occasionally also in combination with thrombi in other chambers. In all of the few instances of thrombi attached to the ventricular wall, there were underlying changes thought to be syphilitic. No specific

changes were noted beneath the atrial thrombi. A large proportion (70 per cent) of those with auricular fibrillation showed mural thrombi.

Pulmonary Thrombosis and Embolism: Blood clots in various stages of organization were found in the lungs of slightly more than one-fourth (34) of the cases. Pulmonary infarcts were usually present (31 cases). Routine dissection of leg veins was not done, so that peripheral thromboembolic disease could not be evaluated. Mural thrombi in the right side of the heart were also present in nearly half (16) of the cases showing pulmonary arterial obstruction. Auricular fibrillation did not appear to increase the incidence of embolic phenomena in our cases. Few pulmonary infarctions were large, and few were recognized during life.

Blood Pressure: A low diastolic pressure was usually but not invariably present. Twenty-seven cases of the heart failure group had coexisting arteriolar nephrosclerosis, and one-half (14) of these maintained a diastolic blood pressure of 80 mm. Hg or above at all times, with constant levels of 100 mm. or more in a few. It was clear that extracardiac mechanisms could in these cases maintain diastolic arterial pressure at normal or high levels despite well developed clinical and pathologic evidence of aortic valve incompetence. On the other hand, it was not unusual for a patient with a diastolic level of 20 mm. or less to exhibit a systolic level of 190 to 200 mm. with neither ophthalmoscopic, renal functional nor renal anatomic evidence of hypertension.

The Clinical Course of Syphilitic Aortic Valve Insufficiency

Throughout the records this group showed a similarity in course that was striking in a disease often marked by its inconsistencies and powers of mimicry. We believe that the clinical course is of equal value in the etiologic diagnosis of syphilitic aortic valve insufficiency to the Wassermann reaction; and where rheumatic heart disease coexists with a positive Wassermann reaction, the clinical course may provide the only clue to etiology. This course may be divided advantageously into four phases:

Phase 1: This is the period from invasion of the aorta to the development of an aortic murmur, and is for the most part the period of syphilitic aortitis. As has been indicated, there is much variability in both its appearance and its duration before complications. After this phase, all tendency to variation appears to cease.

Phase 2: This is the period from the first appearance of an aortic diastolic murmur to the development of the earliest symptoms of cardiac decompensation. From our evidence this period would appear to be both short and asymptomatic. Although many of the patients had been followed in our clinic for various ailments, in only four of the 120 patients had an aortic diastolic murmur been described before symptoms of congestive failure appeared. Additionally, there were only three patients in the entire series of 514 with adequate clinical records who showed the murmur of aortic in-

sufficiency before death from some disease other than syphilitic aortic insufficiency with failure. The past histories were consistently negative with respect to heart murmurs heard during previous physical examinations. From our series, the longest duration of this phase that could be ascertained was three years in one patient and six months in two others. It is our belief that its average duration in the majority of patients is six months or less, and that all will develop congestive failure at the end of it.

Phase 3: This is the period from the earliest symptoms of congestive failure to severe congestive failure. It was most precipitate in development. Nearly three-fourths of our cases progressed from the stage of exertional dyspnea to that of marked peripheral edema in six weeks or less. The transformation of a full-time stevedore to an orthopneic, edematous invalid within one week occurred in several cases. Such a case makes a lasting clinical impression as he lies helpless despite an awesome musculature which has had no time to atrophy.

Phase 4: This is the period from the development of severe congestive failure to death. Once the patient reached this stage, his comfort was almost wholly dependent upon vigorous therapy, and maintenance of compensation without treatment was quite rare, although seven patients were lost sight of for periods up to several years during which the histories did not disclose whether treatment was received.

TABLE II

Length of Life in Months After Onset of Congestive Heart Failure Due to Aortic Insufficiency

Months.....	0–6	6–12	12–24	24–48	48–92
No.	64	24	15	11	6

Duration: The duration of syphilitic aortic insufficiency was short compared to other types of valvular lesions. The tabulation in table 2 shows the length of life in 120 cases after the development of severe congestive failure. The average was about one and one-half years. When this is added to the six months' average of time between the appearance of a murmur and the first onset of failure, the average length of life from the first appearance of a murmur becomes two years.

This suggests that once the media of the ascending aorta weakens in a degree to produce aortic valve incompetence, its further dilatation progresses very rapidly. It should provide a useful point in etiologic diagnosis in patients who show both aortic diastolic murmurs and a positive Wassermann reaction. In the early stages, such etiologic diagnosis is frequently impossible except on a statistical basis of probability from the relative incidence of syphilis and rheumatic fever in the community. But the course of the patient over the next year or so should increasingly narrow down the etiologic probabilities. For example, if a young adult appears with heart

failure and an aortic diastolic murmur and a positive blood Wassermann reaction, but the history discloses that he was turned down by his draft board eight years ago because of a heart murmur, the chances are very slim indeed that he has syphilitic heart disease. Such a patient must be rheumatic or he would not still be alive. We have recently seen in our clinic two patients in whom the diagnosis of syphilitic aortic insufficiency was made 11 and 14 years ago, respectively. Both patients now show aortic valve stenosis and are having their first symptoms of congestive failure, illustrating the usual course of rheumatic valve disease.

Digitalis: There is a current impression that congestive heart failure from syphilis responds poorly to digitalis. This has not been our experience. The initial response to digitalization was often spectacular and usually gratifying. It is true, however, that the rapid progress of the myocardial exhaustion illustrated above results in loss of satisfactory response to digitalis at an earlier stage than is usually found in other types of heart failure.

The "Austin Flint" Murmur: Diastolic murmurs at the apex of the heart were frequently recorded but in the great majority of cases were properly interpreted as arising in the aortic valve. Nevertheless, we have the impression that there is a lingering doubt in the minds of some eminent cardiologists that the so-called "Flint" murmur actually exists. In this connection, it is of interest that four of our cases were described during life as showing low-pitched rumbling apical diastolic murmurs with presystolic accentuation accompanied by a palpable thrill. Two of these cases had been presented by well qualified observers at student and hospital staff conferences as demonstrations of the typical murmurs of mitral stenosis. There is no question in our minds that anyone who makes the diagnosis of mitral stenosis in a patient who has also both aortic insufficiency and a positive Wassermann will be nearly always made aware of his error at the autopsy table.

Heart Size: The average weight of the hearts at autopsy was 600 gm., two of the largest weighing 980 gm. each. Small hearts occurred only with associated extreme coronary ostial stenosis, and it may be inferred that the latter resulted in the patients' death before hypertrophy could ensue.

Anginal Pain: There was only one questionable case who complained of anginal pain in the absence of demonstrable associated coronary artery disease at necropsy. This is in marked contrast to the usual textbook listing of substernal pain as a symptom of syphilitic aortitis. If present, pain would appear to be a symptom of coronary artery involvement, aneurysm or other process than uncomplicated aortitis with or without valvular insufficiency.

Coronary Ostial Stenosis: This was described in 103 (or nearly one-fifth) of our total of 514 cases. The figure may be low, since the milder grades of it were not described before the last 10 years of our study. Over one-half of these patients had an associated aortic valvulitis. Milder degrees

of it had no apparent influence on the duration of life, and none was recognized during life.

Ostial stenosis of severe degree was seen in 19 cases, and occurred almost exclusively in association with aortic valvulitis. Usually there was a clinical picture of frank aortic insufficiency with congestive failure. Over half (10) of the 19 cases were between 20 and 30 years of age, and of these six were females. In all, the sex ratio was 11 males to eight females, and this is the only group in which females appeared with equal frequency with males. The Wassermann reaction was positive in all cases (17) in which it was performed.

Typical anginal pain was present in eight cases but also was associated with congestive heart failure in each instance; it did not appear as an isolated symptom in any case. The duration of life in these patients was significantly diminished, averaging less than four months from the onset of symptoms. The electrocardiograms (standard limb leads and CF_4 in most cases) did not show clear-cut patterns of infarction, and only one case showed a gross myocardial infarct at autopsy. Three patients during life showed right axis deviation, and at autopsy marked narrowing of the right coronary ostia was found in all, with right ventricular hypertrophy present in two of them. Thus the finding of right axis deviation in the electrocardiogram of a patient with syphilitic aortic insufficiency should lead the clinician to suspect right coronary ostial involvement.

The only small hearts in patients with congestive failure were found in this group. The heart weights ranged from 250 to 700 gm., and in general were inversely proportional to the degree of ostial stenosis. The average weight in the group was 505 gm.

Syphilitic Heart Disease in Young Adults: It is customary to regard syphilitic heart disease as primarily occurring in middle age, while rheumatic heart disease affects a younger group. This probably accounts for 20 per cent of our cases of syphilitic aortic insufficiency having been erroneously diagnosed during life as rheumatic. We found a total of 58 cases of syphilitic cardiovascular disease who died before the age of 30 years. Of these, 21 had aortic valve insufficiency and 12 had one or more aneurysms; coronary ostial stenosis was severe in 10 cases; 24 patients died with congestive heart failure, but in 10 of these hypertensive vascular disease appeared to be the major factor.

Associated Rheumatic Heart Disease: This was present in only three cases, or 0.5 per cent of autopsied cases of syphilitic cardiovascular disease.

Miscellaneous: Interesting cases which will only be mentioned include: gumma of the interventricular septum; rupture of an aortic aneurysm into the pulmonary artery, with death from cor pulmonale; a case of combined syphilitic aortitis, rheumatic myocarditis and tuberculous endocarditis; blockage of a coronary artery by a sterile vegetation from a syphilitic aortic valve with myocardial infarction; and a case of complete closure of one cor-

onary ostium, nearly complete closure of the other, and thrombosis of the Thebesian veins.

Discussion

No exhaustive attempt at review of the literature on syphilitic cardiovascular disease has been made, but we have examined certain current beliefs concerning this disease by the correlation of clinical and pathologic findings in a large number of cases. What effect the efficient modern methods of treatment will have on the course of syphilitic cardiovascular disease, only the future will disclose. One of the most important and, we believe, hitherto neglected aspects of the affection is the very rapid downward course of patients after the onset of aortic valve insufficiency. It would appear to be a worth while subject for investigation to ascertain whether this course could be arrested by modern rapid penicillin therapy.

Summary

A clinical survey of 514 cases of syphilitic cardiovascular disease confirmed at autopsy is presented. Auricular fibrillation, bacterial endocarditis, thrombosis and embolism, blood pressure, coronary ostial stenosis and the course of aortic valve insufficiency are discussed.

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CAT SCRATCH DISEASE; NONBACTERIAL REGIONAL LYMPHADENITIS: A REPORT OF 60 CASES *

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CAT Scratch Disease in its most typical form begins with the development of an initial skin lesion a few days following a cat scratch. Rarely there is some other mode of inoculation into the skin. About three weeks later striking enlargement of the regional lymph nodes develops. There may be local redness and tenderness, or the nodes may be virtually insensitive. Fever and systemic symptoms are usually present. The nodes may gradually recede without treatment or proceed to suppuration with the development of pus, sterile on all culture media.

It is the purpose of this paper to report an analysis of 60 cases of Cat Scratch Disease. Twenty-four of these patients were personally studied. The other 36 had intradermal tests by other physicians with antigen supplied by us and proved to have this disease. We are indebted to these colleagues for the data in their cases. Twelve cases were reported previously[1, 2] and are included in this report. In these previous communications we have described in more detail the work of other investigators. This is briefly reviewed here.

Dr. Lee Foshay [3] in 1932 first recognized an ulceroglandular disease entity following the scratch of a cat and referred to it as Cat Scratch Fever. Dr. Franklin M. Hanger [3] and Dr. Harry M. Rose [3] in 1945 prepared an antigen from aspirated pus from a suppurative regional adenitis. Injected intradermally, this gave an intense, tuberculin-like reaction both in Hanger, who suffered from the disease, and in patients of Foshay. Debré,[4, 5, 6] after a visit with Foshay in 1947, began the study of similar cases in France and published the first of his reports of this disease in January, 1950. Mollaret [7-15] in 1950 and 1951 collected many additional cases, found a serologic relationship between this illness and those due to the lymphogranuloma venereum-psittacosis group of viruses, transmitted the disease to one volunteer and to monkeys, and described inclusion bodies in the cells of primary lesions and affected lymph nodes. Greer and Keefer [16] were the first to publish a case in America (1951). Lange [17] has reported three cases unconfirmed by intradermal tests.

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Analysis of Data in Sixty Cases

The disease affected males and females equally. Young people were more commonly affected. The majority of patients were below 20 and a third were below 10 years of age. The patients studied resided in 15 states, Hawaii and Canada.

Fig. 1. Initial lesion on the hand, consisting of a reddish papule surmounted by a vesicle.

Mode of Inoculation: All patients had had contact with cats except for five, who could recall no exposure. In 33 patients there was a history of scratch in the region drained by the affected node or nodes. Three patients had been bitten by a cat. Three patients had circular red papules assumed to be and resembling insect bites prior to adenopathy; all three had had contact with cats. One patient had sniffed cushions contaminated with cat urine; another was pricked by a porcupine quill. One had handled wild rabbits; another was scratched by a splinter on a meat crate. The latter two

denied contact with cats. In 14 patients, the information available was not sufficient to allow conclusions as to the exact mode of inoculation.

We have studied seven small household epidemics involving 16 individuals. Fourteen of these have been children. The other two were a father and a nurse. Each outbreak has centered about the family cat. The

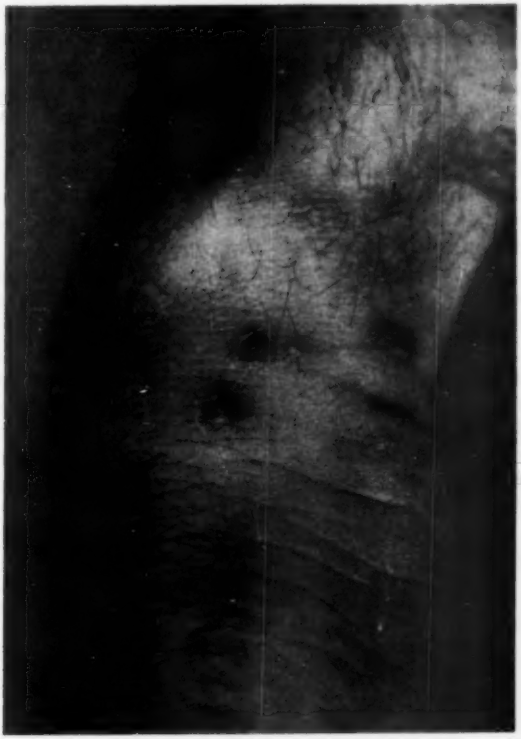

FIG. 2. Multiple initial lesions on the wrist. These are rose-colored papules simulating indolent furuncles.

patients involved have developed the disease over a period of a few weeks and, though the cat was not always dispensed with, other cases have not occurred. This suggests that animals may not be permanently able to transmit infection. The cats suspected in our cases have been healthy animals. The present evidence seems to indicate that these beasts probably transmit the disease only passively, since they have negative intradermal reactions to Cat Scratch antigen. It has been suspected by Mollaret that one of the cat's

natural victims may be the source of infection. It is of interest that the disease is unknown to veterinarians.

The Initial Lesion: Evidence of a primary lesion was found in 28 patients. These usually occurred on unclothed areas of the skin. Seventeen were on the arms, seven on the face and neck and four on the legs.

Several types of primary lesions were observed. Seven consisted of an inflamed scratch. Of these some were inflamed along the whole length, some at only one site. Others were covered by a scab under which a small amount of exudate could be expressed. The primary lesion in some was in the form of a raised purple or dusky red scar. Thirteen consisted of red papules, some resembling small furuncles and others, insect bites. These were solitary in nine instances and multiple in four. Six consisted of a single small ulcer, frequently scabbed or crusted. One case had two purple fang marks; another had a papule surmounted by a vesicle.

In five cases, the patient presumed to remember the time from inoculation to primary lesion; this varied from three to seven days.

Twelve patients felt they were able to date both the inoculation and the appearance of lymph nodes. In half the cases, the interval was between 19 and 28 days; in the remaining patients, the interval ranged from seven to 42 days.

Fourteen patients felt they were able to date the appearances of both the primary lesion and the lymph nodes. In eight cases the interval was between 18 and 30 days; in the other six it was shorter, three to 14 days.

The Lymph Nodes: The lymph nodes most commonly involved were those in the axilla (35). Epitrochlears were involved less frequently (10), and always in conjunction with axillary adenopathy. Lymphangitis was never seen. The nodes about the neck and head were frequently the site of the adenopathy (17). Here the involvement was usually of several different

TABLE I

Mode of Inoculation in 60 Cases

Contact with Cats:	55
Cat scratch	33
Cat bite	3
Insect bite?	3
Sniffed pillows contaminated with cat urine	1
Pricked with porcupine quill	1
No known inoculation	14
No Known Contact with Cats:	5
Scratched on meat crate	1
Handled wild rabbits	1
No known inoculation	3

groups of glands, and was frequently bilateral. The anterior and posterior chains were most frequently affected, but supraclavicular (five), submental (two), submaxillary (three), preauricular (two), and occipital (one) were occasionally involved. Femoral nodes were involved in nine patients. Several times the node affected was in a location not commonly associated with

lymph nodes—under the edge of such muscle as the sternocleidomastoid, the trapezius or the pectoralis.

The nodes were often striking in size—an epitrochlear as large as a golf ball, or an axillary as big as a small orange. In some cases the nodes were rubbery and nontender. More often they were tender, with redness, heat and swelling of the overlying skin. Usually the glands were movable, but some were fixed. These were later found at operation to be involved in suppuration, with sinus tract formation and fibrosis. Suppuration with sterile pus developed in 22 cases.

Data concerning the duration of enlargement in lymph nodes not removed surgically are available in 38 cases. In two weeks, six of the cases had normal appearing glands; in four weeks, 18 cases; in six weeks, 28 cases. In the remaining 10 cases, however, the nodes remained abnormal for periods ranging for from seven weeks to six months.

Systemic Symptoms: Two-thirds of the patients had complaints aside from the adenopathy. The following were common: malaise, anorexia, nausea, weakness, lassitude, aching, chills or chilly sensations and headache. Six patients had a rash associated with the disease; one had pinpoint papules of the upper trunk; another had an erythematous maculopapular eruption of the thumb and index fingers of both hands; four had an eruption resembling measles. In all six, the rash was evanescent, lasting about 48 hours.

Two-thirds of the patients had fever. This was usually mild but in some exceeded 104° F. Absence of fever usually signified lack of suppuration, since only two of the 18 patients without fever had suppuration, and these

TABLE II

Clinical Data in 60 Patients

Number with Initial Lesion	28
Commonest Time Relationships:	
Scratch to primary	3 to 7 days
Primary to bubo	18 to 30 days
Scratch to bubo	19 to 28 days
Regional Nodes Involved:	
Upper extremity	45
Neck	17
Lower extremity	9
Suppuration	22

two had only small areas of necrosis in the node at operation. The 42 patients with fever were evenly divided between those with suppurative and those with nonsuppurative glands. The duration of fever varied from three days to five weeks. In general, there were more fevers of short duration in the nonsuppurative group.

The Intradermal Test: Antigen for the intradermal test has been prepared according to the method devised by Hanger and Rose. The technic of preparation is the same as that of the original Frei test antigen. Aspirated

pus, when found sterile, is diluted 1 to 5 with sterile, isotonic sodium chloride solution and heated to 56° C. for one hour on two consecutive days. After sterility is proved, 0.1 ml. is injected intracutaneously. At 48 hours a positive test shows a central papule 0.5 to 1.0 cm. in diameter, or an area of erythema 1.5 to 6 cm. in diameter, or both.

We have prepared an antigen from macerated necrotic lymph node material removed at operation and found it efficient.

All the patients reported here have had positive intradermal reactions with Cat Scratch antigen. Our early cases were diagnosed with antigen kindly supplied by Foshay, Debré and Mollaret. Later antigen was prepared from material derived from our own patients. Fourteen different antigens have been used; 10 of these have been prepared from pus from the patients here reported. There has been variability in various batches of antigen prepared. Some are strong, giving an intense area of erythema with a dense raised central wheal; others produce only a small area of erythema. There is, too, a considerable difference in intensity of skin reaction of different patients to the same antigen. For example, an antigen injected into one patient produced a raised central papule 1.0 cm. in diameter with an intense surrounding erythema 6 cm. in diameter; in another patient, only a mild reaction with erythema 1 cm. in diameter developed. Moreover, this same antigen injected into four members of a family epidemic of clinical Cat Scratch Disease gave negative reactions in three instances and a positive reaction in the fourth. One of the antigens gave particularly weak reactions and, in fact, gave negative results in two sisters who later responded vigorously to a stronger testing material.

This variation in the strength of different lots of antigen might be expected when one considers the crudeness of the material from which they are prepared. It is planned to try pooling of antigens when the supply permits. It is obvious that each batch of material should be evaluated on known positive reactors prior to placing reliance upon it as a diagnostic tool.

Laboratory Findings: The 41 cases in which leukocyte counts were obtained were nearly evenly divided between those over and those under 10,000 per cubic millimeter. Thirty-two cases fell in the range from 7,500 to 13,000. Only five were above 13,000 per cubic millimeter.

In the 21 cases in which sedimentation rates were obtained, the rate was elevated in 18 cases. In 14 cases, it was between 18 and 38 mm. per hour (Wintrobe).

Cultures of pus from nodes on ordinary media were performed in 19 patients, and were all sterile. In a number, cultures for fungi and tubercle bacilli were also negative. Tularemia agglutinations (27) were negative. Heterophil agglutinations (16) were all within normal limits. Serologic tests for syphilis (28) were negative except in one case with a past history of lues. Frei intradermal tests with Lygranum (24) were negative except in one case.

Complement fixation tests with Lygranum have been performed on the sera of 20 patients. Only five of these have given positive reactions. Serial bleedings, however, have been done in few. In one patient complement fixing antibodies were still present six months and in another two and one-half years after onset. Mollaret [13] has found a much higher incidence of positivity.

One patient with elevation of the serum globulin early in the disease, with return towards normal on recovery, and another with biologically false-positive serologic test for syphilis, have been reported by Bennett and Melton.[18]

FIG. 3. Case 1, showing enlarged suppurative axillary lymph node and positive intradermal test.

Since the disease assumes a variety of forms which simulate most of the diseases of the lymphatic glands, cases illustrative of some of these are being reported.

The form of the disease most commonly encountered by us has been the axillary type, often confused with tularemia.

CASE REPORTS

Case 1. A five year old girl noted a tender mass in the axilla on December 6, 1951. On December 8 a "flea bite" was noted in the right antecubital region. There

was fever of 101° F. She was seen by Dr. Marvin W. Glover, who suspected Cat Scratch Disease. She was very fond of cats, her own and others, and there were numerous scratches on her arms. The leukocyte count was 10,400; heterophil, brucellosis and tularemia agglutinations were negative. The sedimentation rate was 15 mm. per hour (Wintrobe). Chest x-ray was normal except for symmetric bilateral hilar adenopathy. The intradermal test with Cat Scratch antigen resulted in a markedly positive reaction, characterized by a central yellow nodule, 1 cm. in diameter, surrounded by a tender red areola 5 cm. in diameter.

On December 19 the mass, which was now 4 by 6 cm. in size, was removed by Dr. Duane Richtmeyer. The center of the gland was occupied by pus which had penetrated the capsule and formed several sinus tracts in the axilla. The wound healed uneventfully.

The patient later gave a markedly positive intradermal reaction to antigen prepared from her own pus.

Results of Pathologic Examination (Dr. Thomas M. Peery). Gross Description: The specimen consisted of two globular structures said to be lymph nodes from the right axilla. The larger node measured 3 cm. in greatest diameter; the smaller, 0.5 cm. Each was surrounded by adherent fibrous and fatty tissue. On section both contained pus, and were soft and friable.

Microscopic Description: The nodes showed ramifying abscess cavities, lined with a thin layer of fibrous tissue heavily infiltrated with plasma cells and polymorphonuclear leukocytes. Epithelioid cells were evident in some portions of the abscess wall, and a few giant cells containing three to six centrally placed nuclei were also noted. The abscesses contained great numbers of polymorphonuclear leukocytes as well as structureless débris. The surrounding lymphoid tissue showed prominent follicles and moderate reticulum hyperplasia. A few small lesions resembling miliary tubercles were evident in this area; they were composed largely of epithelioid cells and showed a small central area of necrosis, without caseation. The abscess cavities extended also into the fibrous and fatty tissue attached to the nodes. These tissues were more diffusely infiltrated with plasma cells, mononuclear cells and polymorphonuclear leukocytes.

Imprints were stained by Gram's and Giemsa's methods. They showed no bacteria and no unusual granules or inclusions.

The cervical form of Cat Scratch Disease, next most frequent in our experience, may simulate Hodgkin's disease, lymphosarcoma or infectious mononucleosis. The latter was suspected in the following case:

Case 2. An eight year old girl had a rash composed of fine pinpoint papules beginning on December 5, 1951, and lasting several days. On December 7 her mother noticed what appeared to be an insect bite to the right of the patient's mouth. On December 13 a tender lump about 2 by 3 cm. appeared under the middle of the right maxilla. This was accompanied by anorexia, malaise and fever of 103° F. lasting one week. The leukocyte count was 10,150 per cubic millimeter. On December 17 it was discovered that the patient's sister had Cat Scratch Disease. Both were frequently scratched by their pet kittens. The patient's intradermal reaction to Cat Scratch antigen was markedly positive. She was treated with 1 gm. of Chloramphenicol daily for four days. The gland diminished in size so that one week later it was barely palpable.

Tuberculous adenitis of the cervical nodes has undoubtedly been confused in the past with this disease, as happened in the following case. Though previously reported, it bears repetition because of its significance in differential diagnosis.

Case 3. A 48 year old Negro car washer was admitted to Gallinger Municipal Hospital, Washington, D. C., on February 6, 1951. The patient had several cats in his household but denied any scratch. Five days prior to admission pain and swelling developed in the left side of the neck, associated with elevation in temperature to 102° F. Examination on admission revealed a large, tender mass of lymph nodes in the left anterior cervical triangle. These increased in size in spite of administration of 600,000 units of penicillin daily. One node reached a diameter of 5 cm. and became fluctuant. Fever continued. The leukocyte and differential counts, agglutinations for tularemia and brucellosis organisms, and the heterophil antibody titer were normal. Complement fixation test with Lygranum was positive in a dilution 1 to 16. The Kahn reaction was positive. It was at first suspected that the patient had tuberculous lymphadenitis or infected nodes from dental sepsis.

On February 14 about 1 ml. of yellow pus was aspirated from the fluctuant node. This was sterile on ordinary media and on Sabouraud's medium. The pus was diluted one part to five with isotonic sodium chloride solution and heated to 56° C. for one hour on two consecutive days. The patient was given 0.1 ml. of his own antigen intracutaneously, and within 48 hours an area of induration and erythema only 1 cm. in diameter developed. This same material tested on known reactors gave intense reactions. The patient's enlarged lymph nodes gradually subsided. He was discharged on February 26 with only slight residual swelling.

Sometimes lesions of the neck occurring in sites which do not suggest lymph node origin are actually instances of Cat Scratch Disease. The following case simulated infected thyroglossal duct cyst.

Case 4. A seven year old boy frequently played with cats. On August 11, 1951, his father noted a scratch mark on his chin which persisted for several weeks. On September 8 he developed a tender midline swelling, halfway between the thyroid cartilage and the point of the chin. In the next few weeks it grew larger and more tender until, on September 24, he was hospitalized at Bethesda Naval Hospital on the service of Dr. Shirl Winter for diagnostic study. At that time the mass in the midline of the neck was firm, tender and about 5 cm. in diameter. An enlarged node was also noted in the left anterior cervical chain. The leukocyte count was 9,700 per cubic millimeter. The sedimentation rate was 10 mm. in one hour (Wintrobe). Kahn test was negative. The cold agglutinin titer was 1 to 16. Heterophil agglutination was within normal limits. Tularemia agglutination test was negative. Tuberculin test was negative. Coccidioidin and histoplasmin skin tests were negative. X-rays of bones of the jaw and of the lungs were normal.

For 10 days the patient had afternoon fever of 100° F. to 101° F. This was unaffected by aureomycin or penicillin. On several occasions, 1 to 3 c.c. of pus were aspirated and found to be sterile on ordinary culture media. On October 4 an intradermal skin test for Cat Scratch Disease produced a small yellow nodule surrounded by a zone of erythema 2 cm. in diameter. Antigen prepared from pus aspirated from the cervical mass produced negative reactions in controls and positive reactions in persons with known Cat Scratch Disease.

As the patient left Washington, his further course is unknown.

Lymphogranuloma venereum has been confused with this disease on several occasions. The following case is again reported as the best example of this similarity.

Case 5. A 37 year old salesman was admitted to Mount Alto Veterans Administration Hospital, Washington, D. C., on December 29, 1950. On December 7 he

had noted a swollen mass in the right iliofemoral region. This was moderately painful and gradually increased in size, and was accompanied by fever and chills. There was no history of a genital lesion, and none was found. On examination a fluctuant mass was seen in the right femoral triangle, and several other enlarged nodes were noted in this area. The right inguinal nodes were not enlarged, nor were any other nodes. Results of physical examination were otherwise normal. The leukocyte and differential counts, heterophil antibody titer, agglutinations for tularemia organisms and with *Streptobacillus moniliformis*, the Frei reaction and the Kahn reaction were not abnormal. Administration of penicillin, 300,000 units daily for five days, was ineffectual. The suppurative node was aspirated on January 18, 1951, and 30 ml. of yellow pus were obtained. There was no growth on culture; no acid-fast or other organisms were observed on smear, and a guinea pig inoculated with this material was later killed and showed no evidence of disease. The patient was suspected of having lymphogranuloma venereum. When the patient was first seen by us on January 24, there was an elongated mass of nodes running transversely below Poupart's ligament, and in its center were redness and fluctuation. The patient's family owned a cat which occasionally jumped upon his legs, but he recollected no scratches. He remembered having been bitten on the right leg by some insect three weeks before onset of the adenopathy. Two reddish papular lesions had developed at the site of the bites, but no ulceration. These now appeared as slightly pigmented round scars on the right calf. The fluctuant mass was again aspirated and yielded 8 ml. of orange-brown pus, which was sterile on culture on ordinary media and Sabouraud's medium. Cultures for pleuropneumonia-like organisms were negative. The Frei test was repeated and the reaction again found negative. An intradermal test with Cat Scratch antigen gave a strongly positive reaction. On February 1, though the nodes were subsiding, they were removed for study in block by Dr. J. G. Lee. They were sterile on culture for ordinary bacteria and fungi and on special studies for pleuropneumonia-like organisms. The patient has remained well since the nodes were removed.

Results of Pathologic Examination (Dr. John Howe): The surgical specimen consisted of a mass of adipose tissue containing several lymph nodes and an irregular cavity lined by friable reddish-brown tissue and containing a small amount of thick pus.

Microscopic sections through several inguinal lymph nodes revealed large follicles with active germinal centers. The reticulum throughout the nodes was hyperplastic. Other sections showed lymphoid tissue which was largely replaced by granulation tissue containing numerous collections of lymphocytes, occasional polymorphonuclear leukocytes, and rather numerous giant cells of the foreign-body type. Scattered throughout were prominent collections of large macrophages characterized by a large amount of foamy cytoplasm. Several small focal areas of necrosis were present. No typical cellular tubercles or characteristic caseation necrosis was noted. Careful search of sections appropriately stained revealed no acid-fast organisms, inclusion bodies or elementary bodies.

The following case illustrates an extremely mild form of the disease. It is possible that instances of this type are more common than is known, since many such patients may not seek medical care.

Case 6. A 40 year old married woman was seen three days after the development of a faintly tender node in the left groin. There had been no fever and she felt entirely well. On examination a mildly sensitive lymph node about 2.5 cm. in diameter was found in the left femoral region. A smaller gland lay medial to it. There was no redness or increase in skin temperature. On the lower left leg there was a slightly raised erythematous lesion about 1 cm. in diameter. This was surmounted by a dry

scab. Upon questioning the patient it was ascertained that there was a cat in the household, but scratches were not recalled. The initial lesion had developed three weeks prior to the lymph node enlargement. The leukocyte and differential counts were normal except for an eosinophilia of 5 per cent. The sedimentation rate was 18 mm.; complement fixing antibodies for Lygranum were absent from the serum. Positive intradermal tests were obtained with three different antigens. One test showed a faintly raised center with surrounding erythema 2.5 cm. in diameter; another consisted of a slightly raised erythema 1.3 by 1.8 cm., and the third test produced a central nodule 1 cm. in diameter, surrounded by a firm, erythematous area 4 by 6 cm. This illustrates the variability in intradermal reaction to various antigens.

The glands receded rapidly without treatment and in two weeks had disappeared.

Parinaud's oculoglandular syndrome can be caused by Cat Scratch Disease.[19, 20, 21] Peterson [22] has encountered two such cases and proved them with our antigens. The following case is one of those studied by him.

Case 7. A five year old boy played constantly with cats. In February, 1947, he developed a conjunctivitis on the right, with many large folliculi with necrotic centers. Almost simultaneously the preauricular node on the same side became enlarged, tender and rubbery in consistency. The node was about 2 cm. in diameter. The clinical picture was classically that of Parinaud's conjunctivitis. There were no systemic symptoms, and no fever was recorded. Agglutinations for tularemia were negative. Within three weeks conjunctivitis and the lymph node enlargement had gradually subsided without specific treatment. An intradermal test with cat scratch antigen on March 3, 1952, five years after recovery, was strongly positive at 48 hours. At 72 hours the site of the test flared up after partial subsidence and the patient developed 20 to 30 papular lesions like flea bites over the trunk and extremities. These faded within 36 hours.

A brother later developed typical Cat Scratch Disease, with an ulcer on the finger and an enlarged epitrochlear node. His intradermal test was positive three and one-half years after the infection.

As experience accumulates, it seems probable that other variants of the clinical picture will be encountered. Encephalitis in a child with concurrent suppurative disease of the axillary nodes has been encountered by Stevens.[23] The pus on drainage was sterile. An initial lesion at the site of a scratch was noted. Recently an intradermal test was strongly positive. Dr. Robert Debré [5] has encountered three similar cases. The first was a child of 10 who was suddenly seized with convulsions, lapsed into coma and died. Aside from the neurologic manifestations, the only unusual finding was an enlarged suppurative submaxillary node which was treated by incision and drainage. This was proved to be nontuberculous. The patient had constantly slept with cats in his bed. At autopsy there were no gross findings except the residuals of the suppurative node, but histologic studies have not been completed.

The second case was a youth who was seized with convulsions and fever, followed by coma and respiratory difficulty. After four days in a respirator he gradually recovered. The youth had lived intimately with a family of cats and for three weeks there had been a markedly enlarged lymph node at the angle of the jaw. A skin test with cat scratch antigen was strongly positive.

The third case referred to by Dr. Debré was seen with Dr. Laplane. She was a girl of 13 who had inguinal adenitis and suddenly developed convulsions, fever and coma. Recovery ensued. She had had gross contact with cats and there was a positive intradermal test with cat scratch antigen. Complement fixation with Lygranum gave a positive result.

A case simulating chondrosarcoma of the sternoclavicular joint has been described.[24]

Therapy: Though sulfonamides and all antibiotics have been tried, there is no solid evidence that any of these drugs produced curative results. We have the impression that Chloromycetin, given early, may shorten the course of the disease and prevent suppuration. Debré had the same opinion in regard to aureomycin.

Since many cases have been reported in which suppuration and spontaneous drainage lasted as long as six months, it has seemed useful to us to attempt to predict on clinical grounds those cases which might be expected to follow such a prolonged course if not interrupted by surgery. Absence of fluctuation has not always indicated that free pus was not present, since several masses of nodes of firm consistency have been found at operation to contain considerable pus. In general, the combination of several such features as a large mass with local warmth and extreme tenderness with no decrease in size on continued observation, fever of over 10 days' duration, leukocytosis and elevated sedimentation rate suggests suppuration. In several such cases we have attempted to shorten the disease by surgical removal. In each case it has been found at operation that the node is not only suppurative, but also that the pus has dissected through the capsule and formed sinus tracts. The result has been a matted mass of nodes, some of them necrotic and bound together by fibrous tissue. The usual tissue planes have been obliterated and, in the removal of the mass, spurts of pus and blood have been frequent.

There have been no serious complications, however, and the wounds have healed uneventfully.

Pathology: Lymph node material from 20 patients has been obtained either by biopsy or at the time of incision and drainage. The pathologic findings have been comparable to those reported by Debré and Mollaret. These nodes have shown hyperplasia of the reticuloendothelial cells early in the disease, followed by the development of focal granulomata with suppuration and necrosis. Four nodes have now been carefully studied by Dr. Worth B. Daniels, Jr.[25] He states:

"In the four lymph nodes studied microscopically, the findings are essentially in accord with those described by other authors, and even in these few nodes one can distinguish the three phases outlined by Mollaret, namely, the 'elementary' stage of hyperplasia, the 'accentuated' stage with beginning cellular necrosis, and the 'ultimate' stage with the large necrotic foci greatly distorting the architectural pattern of the node.

"Detailed study of our material, moreover, suggests a more concise picture of the pathogenesis of the lymph node changes. In the earliest node studied, reticuloendothelial hyperplasia was present without necrosis or polymorphonuclear infiltration in the capsule and pericapsular tissues. The reaction in these locations then changed, with the hyperplasia giving way to suppuration and necrosis, these changes occurring before any marked effects were noted in either the sinuses or the cords of the medulla. Soon, however, a similar reaction, namely, focal granulomas with and without suppurative centers, appeared in the medulla, and concurrently the cortical in-

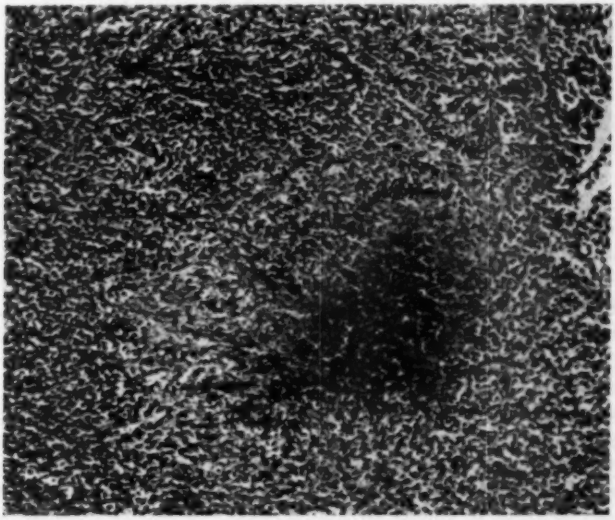

FIG. 4. The later lymph node reaction. A focus of reticuloendothelial hyperplasia in a medullary cord, with central necrosis and cellular debris. Numerous polymorphonuclear leukocytes are present in center of focus, and epithelioid cells form the wide peripheral band. Giant cells are absent.

volvement subsided. Macrophages phagocytosed the necrotic debris, and fibrosis ultimately appeared. Such would seem to be the cycle in nodes which do not suppurate and drain. We would suppose that suppuration and drainage would prolong and accentuate the ultimate distortion of the lymph node architecture and increase the eventual amount of fibrosis.

"Attempts were made to demonstrate microörganisms by use of the periodic-acid-Schiff stain, by MacCallum's modification of Goodpasture's method for staining gram-positive and gram-negative organisms, and by Moran's method for staining tubercle bacilli, but no organisms were demonstrated."

The pathologic pattern is characteristic enough to have suggested the disease to a pathologist, Dr. Theodore Winship, in two cases upon the study of undiagnosed biopsy material. The granular corpuscles within reticulo-endothelial cells of involved nodes described by Mollaret et al.[12] have been demonstrated by Winship [24] in material from one of our cases.

Dr. Charles Armstrong, of the National Institutes of Health, has carried out etiologic studies in those cases where material was available. Macerated nodes or pus, or both, have been injected into a variety of animals and incubating hens' eggs. These studies, while unrewarding at this time, are still in progress. Dr. Armstrong has kindly prepared the various antigens used in our studies. Serologic studies, including complement fixation with Lygranum, have been carried out through his laboratory.

Discussion

Though Foshay first recognized Cat Scratch Disease as an entity, and Hanger and Rose devised a diagnostic skin test in America, French and European investigators[26-50] have carried forward studies of several hundred cases. This work goes far in elucidating the epidemiology, manifestations and causation. It makes clear that the disease is common, ubiquitous, frequently undiagnosed and often confused with other diseases of the lymph nodes. The present report of 60 cases indicates that the disease is frequent and widespread in America and has gone unrecognized. Its frequency is further substantiated by a recent report from Georgia. Bennett and Melton [18] recognized a single case early in September, 1951, and confirmed it by an intradermal test with one of our antigens. In less than two months they had prepared their own antigen and published a report of five cases. When its existence and characteristics are known to the medical profession in this country, the disease will frequently be seen and recognized. Since the disease involves any of the groups of regional lymph nodes, it will be encountered by those in almost all special fields. It can be confused with the lymphomata, tumors, infectious mononucleosis, pyogenic infection of lymph nodes, subcutaneous abscesses, tuberculous lymphadenitis, infected cysts, tularemia, lymphogranuloma venereum and virtually any disease involving the lymphatic nodes. It is important to recognize that nodes in unusual areas may be involved. It has been seen under the edge of the trapezius and pectoral muscles and at the sternoclavicular articulation. It has surely masqueraded as a great variety of lymph node diseases. In any instance of lymph node enlargement of unclear etiology an intradermal test should be done. This will often make biopsy unnecessary and relieve both the patient and the physician of fear of more serious ailments.

It is important that pathologists be cognizant of the lymph node findings since, though the microscopic picture is not diagnostic, it is characteristic enough to suggest the probable diagnosis. This may then be confirmed by intradermal testing.

The antigen for intradermal testing is specific and free of false-positive reactions. Our present experience suggests, however, that a negative test with a single antigen does not eliminate the possibility of the disease. The use of this crude antigen must continue until the etiologic agent is isolated and a more refined material prepared for diagnostic testing.

Conclusions

A series of 60 cases of Cat Scratch Disease from widespread areas in this country has been reported. The entity classically consists of regional lymphadenitis with or without the formation of sterile pus following cat scratch and an initial lesion on the skin. The initial lesion may assume a variety of forms and is present in almost half of the cases. Suppuration with sterile pus occurred in about one third of the patients. Rarely there is no history of cat contact. The disease may simulate any of a wide variety of neoplastic or inflammatory diseases involving regional lymph nodes. The axillary nodes are the most frequent of the regional nodes to be involved, but a cervical form is common. The majority of the patients have a short, mild illness with fever and systemic symptoms, but indolent or suppurative node involvement may persist for months. There is a specific intradermal test. The nodes have a characteristic though not diagnostic microscopic pattern. Present evidence suggests that the disease may be due to a virus related to the lymphogranuloma-psittacosis group.

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SALMONELLOSIS: NINE CASES SUCCESSFULLY TREATED WITH CHLOROMYCETIN *

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Salmonella infections in the United States today still present major problems to the medical profession. The variety of species and the protean nature of the organisms are prime factors in the problem, over 150 different organisms having been described to date. All of these are pathogenic for both men and animals, and can be transmitted from man to man by direct contact, by food contaminated by handlers, improper cooking of infected meat and fowl, foods such as creamy pastries, pies, ice-cream, mayonnaise, eggs (fresh, powdered and frozen), and by mechanical vectors such as fleas and other insects, by contaminated water and parasites, and by cows, horses, foxes, dogs, rats and other animals.[1]

The genus salmonella includes the organisms formerly called "enteric bacteria," the "paratyphoid" organisms and the typhoid bacillus. A few basic biochemical characteristics and a complex antigenic structure bind together this group of organisms. It is not the purpose of this paper to go deeply into this aspect of the problem, but rather to present nine cases of salmonellosis successfully treated with chloromycetin.

The systemic manifestations and characteristics of salmonella infections are manifold. Salmonellosis has been subdivided into the following clinical syndromes:[1]

1. Salmonella fever.
2. Salmonella septicemia.
3. Salmonella enteritis.
4. Localized inflammations, as in the gall-bladder, bones, joints, meninges, urogenital system, etc.
5. Chronic carrier states.

The general mortality rate in salmonellosis is about 6 per cent, varying according to the general physical condition of the patient and the type of organism. The very young and very old are most severely affected, the majority of cases occurring in infants and children. It is also a common complication of old and debilitated individuals.

In the past year, nine patients from whom a salmonella organism has been isolated have been admitted to St. Vincent's Hospital (primarily for private patients), in Indianapolis, Indiana. These organisms have been recovered from the blood, stools and localized abscesses. In all cases, the organism has been finally identified as to type.† None of these patients

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was diagnosed prior to admission to the hospital, and all were ill enough to warrant hospitalization.

Case Reports

Case 1. A 21 month old colored boy was admitted September 20, 1950, with a history of "stomach ache" for 24 hours. He had been given castor oil. This was followed by four liquid stools in 12 hours. He previously had been in good health. On admission his temperature was 104.6° F., pulse 160, and respirations 40. Ears, nose, throat and lungs were negative. Generalized abdominal tenderness and rigidity were present. The patient was taken to surgery for an appendectomy, where it was noted that there were large mesenteric nodes present. The distal six inches of ileum were distended and thickened. Enlarged lymph nodes could be palpated in the wall of the bowel. After surgery, bloody diarrhea persisted. His temperature was 105° F. the first day. Stool and blood cultures on September 21 were both positive for a gram-negative bacillus later identified as *S. typhosa.* Agglutinations for typhoid O and H were positive in dilution of 1:160; all others were negative. The patient was started on chloromycetin on September 22. His first afebrile day was September 26. He had bloody mucous stools until September 27, and green, mushy, seedy stools until October 8. Agglutinations for typhoid O and H were positive in dilution of 1:128 on October 2. Stools were negative on October 3, 4 and 5, and blood culture was negative on October 5. The patient was dismissed as recovered on October 11, the twenty-second hospital day. He received a total of 13,000 mg. chloromycetin over an 11 day period.

Case 2. A four year old colored female, sister of case 1, was admitted October 13, 1950, with a history of having had a cold and fever for one week. She had been given penicillin shots at home. There was no history of diarrhea, but she had a "stomach ache." Her temperature was 103° F. A physical examination revealed a distended abdomen. The liver was palpated 3 cm. below the right costal margin. The spleen was not palpated. Her white blood count was 3,500, with 72 per cent lymphocytes. On October 13 the stool culture was negative, and a blood culture was positive for *S. typhosa.* Agglutinations for typhoid H were positive in dilution of 1:80, and O was positive 1:160. All stool cultures were negative. Subsequent blood cultures were negative. Agglutinations on October 23 gave typhoid H positive 1:80, typhoid O positive 1:640. The patient received chloromycetin for 18 days and the total dosage was 18,250 mg. She was dismissed on October 31 as recovered. Subsequent rechecks in the out-patient department were normal.

Case 3. A 44 year old white male, a traveling burlesque comedian, was admitted on May 13, 1950, with a history of chills and fever for one week. He had been in another midwestern hospital for four weeks prior to this with diarrhea, cough, chills and a fever up to 105° F. At that time stool cultures and heterophil, cold and enteric agglutinations were normal. He received no specific therapy and his temperature returned to normal. On admission to this hospital the positive physical findings were those of a thin man with generalized lymphadenopathy and slight liver enlargement. Temperature was 100.4° F.; pulse, 94. Hemograms and repeated urine examinations were normal. Sedimentation rate was 40 mm. per hour. Heterophil and all enteric agglutinations were again negative. Chest x-ray and complete gastrointestinal x-rays, including gall-bladder, were normal. Stool culture on May 15 was positive for *Salmonella bareilly* (reported on May 23). Biopsy of axillary lymph node revealed reactive lymphadenitis. Temperature spiked daily to 103° F. The patient was started on chloromycetin on May 23 with a drop in temperature to normal within 24 hours. He was dismissed on the fourteenth hospital day, afebrile and still receiving chloromycetin. Subsequent stool cultures were negative. He received a total of 18,000 mg. of chloromycetin. Further follow-up care was not possible.

Case 4. An 11 month old white male was admitted on October 14, 1950, with a history of vomiting and severe diarrhea for the past 24 hours. There was no cramping and no blood in the stool. Physical examination revealed an acutely ill, dehydrated male infant. Further examination was non-informative. His temperature was 104° F. White blood count was 4,300, with 62 per cent lymphocytes. Carbon dioxide combining power was 30 vol. per cent. Stool culture revealed salmonella organisms later identified as *S. pullorum.* The child was given fluids, penicillin and aureomycin intravenously on the first day, and chloromycetin on the second day. The temperature remained normal after the second day. He received a total of 5,300 mg. chloromycetin.

Case 5. A 19 month old white female, en route through this city from New York, was admitted on September 29, 1950, after having had a convulsion in a doctor's office. She had had an upper respiratory infection for three days. There had been no diarrhea or vomiting. Temperature was 103° F. Physical examination revealed a mild nasal congestion. Throat, ears, chest and abdomen were negative. During the first hospital day she began having frequent loose yellow stools, which persisted. Temperature was up to 104° F. for the next two days. White blood count on admission was 5,400, with 62 per cent lymphocytes. Blood culture on September 30 was negative in 24 hours, but *S. typhimurium* was isolated at 48 hours. Stool culture on September 30 was positive for salmonella organisms, later identified as *S. typhimurium.* Chloromycetin was started. After 48 hours, fever and all symptoms abated. The patient received a total of 4,200 mg. chloromycetin.

Case 6. A 50 year old white male was admitted on June 2, 1950, with a history of nausea, vomiting, diarrhea, chills and fever for 36 hours. He had drunk well water 10 days prior to admission while visiting out of the state. Temperature was 103° F., and pulse was 84. The only positive physical finding was hyperactive bowel sounds. White blood count was 5,200, with 26 per cent lymphocytes. Agglutinations on June 2 and June 10 were positive in a dilution of 1:40 for paratyphoid B. Stool culture on June 3 grew *S. typhimurium.* He was started on chloromycetin and was afebrile after the fifth hospital day. He received a total of 17,000 mg. chloromycetin in the hospital and was dismissed asymptomatic, still on the drug. Follow-up stool culture on June 28 revealed no pathogens. All agglutinations were negative.

Case 7. A 53 year old white male was admitted on July 12, 1950, with a history of a loss in weight of 35 pounds, and intermittent chills and fever since January. He had had pneumonia with pleural effusion on the right in January. There was one episode of diarrhea in March. In June the patient became jaundiced. Physical examination showed an emaciated white man, acutely ill, with a temperature of 103° F. Liver was palpated 5 cm. below the right costal margin. White blood count was 46,000, with 90 per cent polymorphonuclears. Total serum bilirubin was 2.95 mg. per cent. Agglutinations for typhoid O and H, paratyphoid A and B were all positive in 1:80 dilution. Total serum proteins were 5.19 gm. Cephalin flocculation was 4 plus at 24 hours. Blood culture drawn on July 12 grew *S. typhimurium,* and stool culture on July 15 gave the same organism. He was treated with blood transfusions, fluids, supportive measures and chloromycetin. His course was stormy. On September 26 he was taken to surgery, where a large liver abscess was drained from which a positive culture for *S. typhimurium* was obtained. The same therapy was continued. The patient was dismissed on October 5, 76 days after admission, in good condition and asymptomatic. He had received a total dosage of 170,500 mg. chloromycetin.

He was readmitted on December 11, 1950, with weakness, fever and a productive cough. Roentgenogram of the chest revealed a large circular density surrounding the hilum posteriorly in the right chest. Open drainage yielded a large quantity of

dark yellow pus, which was sterile. Blood cultures were negative. He received 28,500 mg. chloromycetin on this admission. He was dismissed afebrile on December 29.

On the third admission, January 5, 1951, he had a temperature of 103° F., profuse diaphoresis, and signs of peripheral neuritis in both legs. He stated that he had felt feverish, but when his cough became productive his fever subsided. Bronchogram revealed a small cavity in the anterior part of the middle lobe. He was treated again with chloromycetin, and terramycin was added, with a gradual improvement in his condition. Subsequent follow-ups have indicated no return of any symptoms which could be attributed to salmonellosis, and all cultures have remained negative. His total dosage of chloromycetin was over 271,000 mg.

Case 8. A 44 year old Jewish housewife was admitted on May 21, 1951, with complaints of six to 10 soft-to-liquid stools daily for the past week, accompanied by nausea, vomiting and abdominal cramping. There was no blood in the stools. She had recently returned from a trip through the Southern states. Physical examination revealed a temperature of 98.8° F., and a pulse of 84. The remainder of the examination showed nothing important. White blood count was 6,500, with 34 per cent lymphocytes. Sulfasuxidine was given, 3 gm. every four hours. Blood culture was negative. Stool culture was positive for *S. typhimurium.* Plate sensitivity showed this organism sensitive to chloromycetin, terramycin and aureomycin, in that order. Chloromycetin was started on May 25, and the sulfasuxidine was discontinued. The highest temperature during her entire hospital stay was 100° F. Diarrhea persisted for seven days. Stools remained positive for *S. typhimurium* until June 11, 1951. Roentgen studies of the stomach and colon were normal. Gall-bladder failed to visualize on repeated examinations. Agglutinations on May 23 showed typhoid H, 1:20; typhoid O, 1:40; paratyphoid A and B, negative. Liver function tests were within normal limits. Total chloromycetin dosage was 22,000 mg.

Case 9. A nine month old white male was admitted May 10, 1951, with a severe diarrhea and fever up to 106° F. of one week's duration. There was blood in the stool on one occasion. He had had two doses of penicillin because of concomitant tonsillitis. Physical examination revealed tonsils that were large and reddened, a distended abdomen and excoriated buttocks. White blood count was 13,800, with 49 per cent lymphocytes. Stool culture was positive for *S. typhimurium.* Agglutinations for typhoid O were positive only in dilution 1:20. Blood culture was negative. Chloromycetin was given. Diarrheic stools continued for one day and gradually diminished in number. He became afebrile on the fourth hospital day. Total chloromycetin dosage was 2,500 mg.

Discussion

Etiology: In the nine cases presented, *S. typhosa* was the causative organism in two cases, *S. typhimurium* in five, *S. bareilly* in one and *S. pullorum in one.* (Salmonella organisms frequently isolated in this country are *S. paratyphi A* and *B, S. typhimurium, S. derby, S. paratyphi C, S. choleraesuis, S. montevideo, S. oranienburg, S. newport, S. panama, S. anatium, S. give* and *S. suipestifer.*) This corresponds to the work of Edwards, Bruner and Moran, who isolated 12,331 cultures from 47 animal species. They found *S. typhimurium* more frequently and in a greater number of animal species than any of the other types.[2] As seen in table 1, this organism accounted for over half the number of cases in the above series.

TABLE I
Nine Cases of Salmonellosis

Blood Culture	Stool Culture	Agglutinations (Highest Titer)	Extraintestinal Localizations	Diarrhea	Highest Temp.	WBC	Drug Used	Clinical Type
1. *S. typhosa*	*S. typhosa*	Typh. H—1:160 Typh. O—1:160 Para. A—Neg. Para. B—1:80	None	Moderate	105°	12,200	Streptomycin 13,000 mg. chloromycetin	Typhoid fever and septicemia
2. *S. typhosa*	Negative	Typh. H—1:80 Typh. O—1:640 Para. A—1:20 Para. B—1:20	None	None	104.4°	3,500 72% lymphs	18,250 mg. chloromycetin	Typhoid fever and septicemia
3. Negative	*S. bareilly*	All negative	None	None	103°	7,500 41% lymphs	18,000 mg. chloromycetin	Salmonella fever
4. Negative	*S. pullorum*	All negative	None	Severe	104°	4,300 62% lymphs	Penicillin Aureomycin 5,300 mg. chloromycetin	Gastroenteritis
5. *S. typhimurium*	*S. typhimurium*	All negative	None	Moderate	104°	5,400 62% lymphs	4,200 mg. chloromycetin	Gastroenteritis and septicemia
6. Negative	*S. typhimurium*	Para. A—Neg. Para. B—1:40	None	Moderate	103°	5,200 26% lymphs	17,000 mg. chloromycetin	Gastroenteritis
7. *S. typhimurium*	*S. typhimurium*	Typh. H—1:40 Typh. O—1:40	Liver abscess Lung abscess	None	105°	46,000 90% polys	Over 271,000 mg. chloromycetin	Septicemia and extra-intestinal localization
8. Negative	*S. typhimurium*	Typh. H—1:20 Typh. O—1:40	None	Severe	100°	6,500 34% lymphs	22,000 mg. chloromycetin	Colitis
9. Negative	*S. typhimurium*	Typh. O—1:20	None	Severe	106°	13,800 49% lymphs	2,500 mg. chloromycetin	Gastroenteritis

S. pullorum is rarely found in humans, but in case 4 we felt that this was a definite pathogen. None of the cases described was part of an epidemic, although cases 1 and 2 were in the same family and their illnesses were close together. In none of the nine cases could the vector be determined, although an attempt was made in each instance. With the exception of cases 1 and 2, there was no history that any other member of the family became ill at the same time, which is usually true in most outbreaks of salmonella "food poisoning."

Pathogenesis: That salmonellosis is extremely protean in nature is emphasized by the number of clinical syndromes associated with it. In nearly all cases, entrance is gained via the alimentary tract. Blood stream invasion frequently occurs early in the course of the disease. Why some patients will develop a gastroenteritis or enterocolitis while others will develop septicemia or salmonella fever due to the same organism is not yet known. For example, *S. typhimurium* produced only signs of colitis in case 8, a 44 year old housewife in good health prior to her illness. In cases 5 and 9, however, both patients were severely ill with diarrhea and high fevers, and 5 had septicemia. Case 7 had septicemia with at least two known extraintestinal localizations. It has been theorized by many writers that the age and general physical condition of the patient influence to a great extent the course the disease process might take. This certainly seems to be borne out in these patients. In case 7, the man had been ill six months prior to admission. It is not known if his pneumonia with effusion in January was due to a salmonella or some other organism. Likewise, it is not known if the jaundice he described in June was on a basis of viral hepatitis or if it was due to infiltration of salmonella organisms. At any rate, he had obviously been ill over a long period of time and was debilitated at the time of his admission. Case 8 exhibited a relatively benign form of salmonellosis and, if one chooses to agree with the concept that pathogenesis depends on the age and general physical condition of the individual, it can be noted that she was middle aged and in good health. Thus, one would not expect the more serious manifestations from the same organism. Cases 5 and 9 exhibited severe forms of enterocolitis and occurred in very young children.

It can be seen from table 1 that there was only one instance of extraintestinal localization. This occurred less often than expected. Although the total number of cases is limited, it suggests that relatively early institution of specific therapy may have aided in preventing this complication in the remaining eight cases.

Symptomatology: Symptoms depend upon the course of the disease process. Cases 1 and 2 were rather typical of typhoid fever, which in itself is a classic example of a severe enteric fever. The onset was rather insidious in both patients. In case 2 it started with a pharyngitis. Painful abdominal cramps and distention were prominent in both, but diarrhea was present in only case 1. High fever and prostration were present in both. The fever usually remains elevated for three weeks or more in severe cases, but

both cases 1 and 2 fell to normal within five days after therapy was started. Leukopenia was present in one patient, mild leukocytosis in the other.

Salmonella fever due to other organisms of the salmonella group is similar to that of typhoid fever but is usually of a milder degree, and complications such as hemorrhage or perforation of the bowel occur less frequently. It must be remembered, however, that these other salmonella types can produce acute, severe illnesses and may even prove fatal.

Symptoms of the gastroenteric form of the disease may range from a rather mild innocuous form of diarrhea, as in case 8, to severe vomiting and diarrhea with acidosis, as seen in case 4. This may be a part of the enteric fever or may occur independently and produce no other systemic manifestations. The milder form often progresses into the nonsymptomatic carrier state and may never be recognized clinically as a form of salmonellosis. The most common example of this type is probably the epidemic form of salmonella food poisoning, which is usually rather mild and short in duration but also may terminate fatally.

Symptoms of the septicemic group are similar to septicemia produced by many other bacteria. The onset of illness is usually abrupt, with chills and fever and moderate to severe prostration. Diarrhea may or may not be present prior to or coincident with the chills and fever. Other symptoms depend on the site of extraintestinal involvement, and practically every organ in the body has been described as a site of localization. In the series of 2,949 cases of human salmonellosis described by Edwards, Bruner and Moran, the organisms were isolated from the spinal fluid, urine, empyema pus, peritoneal pus, gall-bladder, endocardium, lymph node, prostate, uterus, sinus, tonsil, periosteum, joints and wounds.[2]

Case 7 represents one of the more unusual sites of localization, in the form of a large liver abscess and multiple lung abscesses. Although liver abscess is a rare complication of salmonellosis, it was feared that this patient might die of hepatic failure, as is occasionally seen in acute viral hepatitis. Thus, it seems logical that in cases of unexplained hepatitis, routine stool cultures and blood cultures for salmonella organisms should be done.

Diagnosis: The diagnosis of salmonellosis should be reserved for those cases in whom the organism can be successfully cultured and positively identified as one of the salmonella group. In all nine of our cases, the organism was successfully cultured from either the stool, the blood or extraintestinal localization. All cultures were tentatively identified as salmonella in our laboratory by their group specific biochemical and serologic reactions. The stool cultures were obtained in the ordinary manner, the only precaution being to keep the specimen near body temperature until it reached the bacteriologist. Lomberg [3] reported that 77 per cent of 61 strains of salmonella were retarded by sodium sulfate and 8.2 per cent were retarded by magnesium sulfate. So it can be concluded that saline purges are contraindicated for obtaining stool cultures.

It is of interest to note that routine agglutinations of enteric organisms were of aid in diagnosis only in the cases of typhoid fever. Even in cases 3 and 7, which we assumed to be of rather long standing, the agglutination titers were not significant. This can be explained by the complex antigenic structure of this group of organisms described by Kauffmann and White. This makes cultural diagnosis of even more importance in this disease process.

Treatment: All nine cases were treated with chloromycetin, the individual doses being tabulated in table 1. In all patients there seemed to be a prompt improvement of all symptoms except in case 7 where progress was much slower and where open drainage of abscesses was later carried out. The two cases of typhoid fever made a much more rapid recovery than is ordinarily expected. The response of the fever in case 3 was dramatic, but could have been coincidental. Unfortunately, further follow-up studies on this patient have been impossible because of his occupation. Cases 4, 5, 6 and 9 were markedly improved after 48 hours of chloromycetin therapy. All cases had a complete clinical recovery. Follow-up out-patient examinations and cultures were normal except in cases 3 and 5, who were transients and could not be followed.

Jackson et al.[4] performed in vitro sensitivity tests on strains of salmonella and found the order of diminishing activity on a weight basis was polymyxin, aerosporin, chloromycetin, penicillin, aureomycin, streptomycin and bacitracin. Kurz, Crehan and Thomson found streptomycin to be of no value in a fatal case of salmonella endocarditis.[5]

Felsenfeld and his co-workers concluded that streptomycin was generally ineffective in treating salmonellosis.[6] Other clinicians have found the sulfonamides to be of no value for this organism.

Plate sensitivity tests done in our laboratory on two of the isolated cultures revealed them to be most sensitive to chloromycetin, to a lesser degree to terramycin and aureomycin, and resistant to penicillin, streptomycin and bacitracin.

Although it is felt that chloromycetin is the basic feature of the proper management of salmonellosis, correction of fluid balance and dehydration along with acidosis is of the utmost importance. Blood transfusions may be necessary, especially in the very young and in the debilitated individuals who suffer from prolonged infection.

Summary and Conclusions

Nine cases of salmonellosis successfully treated with chloromycetin are presented and the literature is briefly summarized. All of these occurred sporadically over a period of one year. The patients, acutely ill, were admitted to a private hospital in Indianapolis. One represented an example of salmonella fever and four salmonella septicemia. Only five patients manifested acute salmonella enterocolitis; one had extraintestinal localizations.

The diagnosis of salmonellosis in each instance of the infection was made by isolating the organism from the blood, the stool or from extraintestinal purulent localization. The organisms were finally identified by specific type. Two patients with typhoid fever (*S. typhosa*) represented the only ones with diagnostically significant blood agglutination titers. Other causative organisms were: *S. typhimurium*, *S. pullorum* and *S. bareilly*. *S. typhimurium* occurred in half the cases. Follow-up clinical examinations and cultures were done in seven available cases. These patients remained completely cured.

Salmonella infections in man constitute a major medical problem. Over 150 strains have been described as pathogenic for both animals and man. The commonplace occurrence and easy transmissibility of the organisms are well known. It is hoped that chloromycetin or newer antibiotics will aid in lowering the mortality, morbidity and incidence of salmonella infections.

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THE PREANESTHETIC INDUCED COUGH AS A METHOD OF DIAGNOSIS OF PREOPERATIVE BRONCHITIS *

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Three years ago we started asking each patient to cough during the first few minutes of spinal anesthesia to observe the ascent of muscular paralysis of the abdominal wall.[1] We were surprised to hear a clearly "wet" cough in many patients who had a normal respiratory tract according to the history and physical and roentgenologic examinations recorded in the hospital chart. When we extended the practice and requested a voluntary cough of every patient before the induction of any method of anesthesia, an apparent abnormality of the sound of the cough was quite commonly heard. It was not known, however, which of these sounds could be interpreted as evidence of tracheobronchial disease. This investigation was initiated, therefore, to determine the significance of these sounds and the reliability of the preanesthetic induced cough as a method for the diagnosis of bronchitis before operation.

Method and Material

From September 1, 1950, to August 31, 1951, we examined 1,821 patients in an unselected and roughly consecutive series of elective and urgent cases in the operating rooms of two general hospitals serving largely the lower middle class income group. A majority was scheduled for elective surgery; this fact reduced the number with acute respiratory infections. All patients for tonsillectomy, pulmonary lobectomy and other operations performed because of respiratory disease were omitted from this study. We also studied several hundred other individuals; some were non-patients and others were patients chosen to form special groups for separate consideration, as described later.

Each subject was urged to cough vigorously unless an incarcerated hernia or ruptured viscus was suspected. The patient was asked to cough when he was lying on his side or sitting, because such a cough was more effective than if he was in the supine position. The cough was elicited early in the preanesthetic examination, before the patient had a chance to clear his respiratory passages consciously or unconsciously. The sound of the cough was evaluated at a normal conversational distance; the chest was not auscultated at the time. The patient was urged to cough vigorously and was

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inspected to be certain that he was exercising a forceful contraction of the anterior and lateral abdominal walls after a deep inspiration. If the patient was not instructed he often would simply clear his throat or produce a shallow cough or grunt. An unsatisfactory cough was the rule when the cough was painful or if the patient was depressed by premedication or debility. If the examiner persisted, however, the patient almost always eventually coughed satisfactorily, except in the presence of a severely painful thoracic or abdominal condition. Even three year old children were able to cough on request, in imitation of our own effort as an example of what was desired. When premedication or illness excessively depressed the nervous system the patient was uncoöperative; such instances were rare and were not included in the tabulation.

The induced cough of each patient was classified by its pattern of abnormality *before* the data of the history, physical and x-ray examinations were obtained to be correlated with our interpretation of the induced cough.

Every induced cough was classified as normal or abnormal. A normal cough was a single, brief, bechic blast that sounded "dry" and clear, was not easily produced and was not "self-propagated." An abnormal cough was described as either "wet" or "dry." The degrees of "wetness" were mild, moderate and marked: mild, if râles or rhonchi disappeared immediately with a brief cough without obvious expectoration or swallowing; moderate, if the adventitious sounds were removed only by repeated coughing or obvious expectoration or swallowing; marked, if the abnormal sounds persisted after repeated and vigorous coughing. A "dry" cough was considered mild if the request to cough resulted in a short paroxysm of "dry" or hoarse coughing, clearly "self-propagated," without a deliberate effort behind each blast. Moderate and marked degrees of a "dry" cough were of the same pattern but correspondingly longer in duration. When "wetness" was present this characteristic was considered more important than the paroxysmal pattern or the duration of the cough in classifying its severity.

Several observers could almost always agree on the presence or absence of an abnormality in the sound and pattern of a voluntary cough. A vigorous ("belly") cough was required for certainty in many mild cases, especially when the patient was depressed or feeble or when the cough was "dry." Variations were occasionally found among observers of the same patient in classifying the cough as "moderate" instead of "marked," or vice versa. On the whole, however, patients were grouped similarly by the members of the anesthesia department after a little experience, because the patterns of abnormal sounds on coughing were simple, few and regularly reproducible.

The recognition of "wetness," hoarseness or "self-propagation" of the preanesthetic induced cough is facilitated by the following factors which favor the retention of secretions just before the induction of anesthesia:

1. Surgical diseases are often attended by abdominal pain or distention which interferes with coughing.

2. The patient is almost always continuously confined to bed for several hours or a night prior to his arrival in the operating room.

3. Sedative or preanesthetic medication which obtunds the cough has usually been administered an hour or more earlier.

4. The routine preoperative minimization of such functions as defecation, talking and walking produces a marked curtailment of the vigorous respiratory movements which aid ciliary cleansing of the bronchial tree.

Results

A. The significance of abnormalities of the cough voluntarily produced just before anesthesia is evident from the high degree of correlation that exists between such abnormalities and disease of the tracheobronchial tree.

1. In a group of 100 patients with known disease of the lower respiratory tract, proved by historical, physical or roentgenologic evidence, 95 per cent were judged to have an abnormality on induced coughing. The exceptions, i.e., the "false normals," were patients with severely painful diseases which splint the upper abdominal muscles, and patients with mild pulmonary congestion due to left ventricular failure, or with mild "dry" chronic bronchitis or bronchiectasis or bronchial asthma in remission.

2. In a group of 200 adolescents known to be free of respiratory disease the induced cough was never abnormal to a "moderate" or "marked degree"; rarely, a "mild" abnormality would be found.

Table I

Tabular Summary of Data Presented above in Paragraphs A 1–4

No. of Patients	Preop. Respiratory Status	Type of Induced Cough	
		Abnormal	Normal
100	With known resp. disease	95 per cent	5 per cent
200	Healthy adolescents	2 per cent	98 per cent
	Type of induced cough	Preop. resp. disease proved by history, physical or x-ray data	
500	Normal	Found in 2 per cent	
200	Mildly abnormal	Found in 95 per cent	
200	Moderately or markedly abnormal	Found in 100 per cent	

3. Among 500 patients with a normal response to our request to cough, only 2 per cent were later found to have a diseased respiratory tract by history or by physical or roentgenologic data. "False normals" were associated with the conditions mentioned in paragraph 1 above.

4. Among 400 patients classified as having an abnormal induced cough, subsequent study of the patients obtained confirmatory evidence of respira-

tory disease in all subjects with a "marked" or "moderate" cough, and in 95 per cent of those with a "mild" abnormality. In 90 per cent of all patients with an abnormal cough, our detailed questioning elicited a history of excessive sputum and expectoration, usually confined to a short period after awaking from sleep. This fact was absent from the hospital histories of a vast majority of these patients. It was usually not considered a noteworthy symptom of abnormality by the patient even when it was called to his attention. In only 7 per cent of abnormal coughs were roentgenologic or physical signs present to confirm the presumptive diagnosis of tracheobronchial disease suggested by the abnormality on voluntary coughing.

B. The significance of abnormalities of the induced cough has been corroborated by another method, based on the truism that a preoperative bronchitis predisposes to a postoperative respiratory complication. If the abnormalities we recorded are really representative of an underlying pathologic state of the tracheobronchial tree, there should be a high degree of correlation between these abnormalities and postoperative respiratory complications appearing within the first three days. Proof of this relationship is provided by the following data:

1. In 104 gastrectomies there were 39 instances of definite postoperative respiratory disease (32 of bronchitis, two of atelectasis, two of bronchopneumonia, two of severe bronchitis or transient atelectasis, and one of asthma). Abnormalities of the preanesthetic induced cough were recorded by the anesthesiologist in 35 instances (90 per cent) of these 39 respiratory complications. It is significant that the abnormalities of the induced cough were so obvious as to be classified as "marked" in 24 and "moderate" in two; they were "mild" in only nine patients.

2. Among these 104 gastrectomies there were 45 patients who recovered without a cough or any other sign of a respiratory complication. Only six instances (13 per cent) of these 45 uncomplicated recoveries had an abnormality of the induced cough; five were "mild" and one was "marked." The incidence of abnormalities of the induced cough in this group of 45 gastrectomies was significantly smaller than in the group that developed respiratory complications.

3. The remaining 24 patients in this group of 104 gastrectomies had a mild and transient postoperative cough. Although it was not classifiable as a significant complication, the cough was a distinct sign of an abnormally hyperirritable and hypersecreting respiratory tract when viewed in the light of the 45 recoveries mentioned in paragraph 2 above which were not complicated by even a mild cough. Nine instances (38 per cent) of the 24 gastrectomies recovering with only a mild and transient postoperative cough had an abnormality of the induced cough; of these nine abnormalities, four were "marked" or "moderate," and five were "mild."

4. In 123 biliary surgical patients with a normal induced cough there were no postoperative respiratory complications in 114; bronchitis occurred

in seven and atelectasis in two. The two instances of atelectasis occurred in patients with severely acute cholecystitis; in addition, one was moderately obese and the other markedly emphysematous. These factors, which interfered with their ability to cough just before anesthesia, caused these patients to be erroneously classified among those with a normal induced cough early in our study, before we were aware of the conditions which produce "false normals." Similarly, in the seven bronchitides, there were two patients with acutely painful cholecystitis, two with marked obesity, and one who aspirated stomach contents during recovery from anesthesia.

5. In 39 biliary surgical patients with an abnormal induced cough, postoperative respiratory complications were absent in 13; bronchitis occurred in eight, atelectasis in 13, and either atelectasis or severe bronchitis in five. Thus the incidence of significant postoperative complications was 67 per cent among the 39 biliary patients with an abnormal induced cough before anesthesia, but only 7 per cent among the 123 biliary patients with no cough abnormality. This difference is of great statistical weight even without correction for such factors as "false normals" and aspiration of gastric contents, which unfairly loaded with postoperative respiratory complications the "normal" group described in paragraph 4 of section B.

TABLE II

Tabular Summary of Data Presented above in Paragraphs B 1–6

	Type of Induced Cough	
Gastric Patients	Abnormal	Normal
39 gastrectomies with postop. resp. complications	90 per cent	10 per cent
45 gastrectomies without postop. resp. complications	13 per cent	87 per cent
24 gastrectomies with postop. mild cough	38 per cent	62 per cent
Biliary Patients	Postop. Resp. Complications	
123 with normal induced cough	Found in 7 per cent	
39 with abnormal induced cough	Found in 67 per cent	
Gastric Patients		
66 with normal induced cough	Found in 24 per cent	
63 with abnormal induced cough	Found in 90 per cent	

6. We similarly analyzed another two groups of patients who had had a subtotal gastrectomy. (These included only a few of the gastrectomies discussed above in paragraphs 1–3 of section B.) Sixty-three had an abnormal induced cough before anesthesia; 57 of these (90 per cent) developed a cough or more serious respiratory complication. Sixty-six other gastric surgical patients had no abnormality on preanesthetic voluntary coughing; only 16 of these (24 per cent) developed a cough or more serious respiratory complication.

C. The incidence of an abnormal induced cough in the general run of all adult patients arriving in our operating rooms is surprisingly high. Careful analysis of our findings reveals, however, that its great frequency does not

warrant the assumption that abnormalities of the preanesthetic cough are so common that they have no significance. The following tabular analysis clarifies this point.

A subsequent paper will present and discuss the great frequency and hazard of cigarette smoking with regard to the occurrence of postoperative respiratory complications. It must be mentioned here briefly, however, to explain the high incidence of an abnormal induced cough found among adult males. By segregating the group of nonsmokers, we can observe that

TABLE III

Series of 1,821 Consecutive Patients	Incidence of Abnormal Cough
1,031 adult females (smokers and nonsmokers)	20 per cent
629 adult males (smokers and nonsmokers)	46 per cent
336 nonsmoking adult females	8 per cent
147 nonsmoking adult males	14 per cent
70 female children	12.7 per cent
91 male children	13 per cent

an abnormal induced cough is truly an uncommon finding in the nonsmoking general population. Only then can we appreciate that an abnormality of the induced cough in reality represents an unhealthy state of the tracheobronchial tract, even though it is so common in adult males. The 8 to 14 per cent incidence of abnormal induced cough in the nonsmoking population is largely and readily attributable to clinically apparent respiratory infections.

In recapitulation, we have found the following relationships to exist between an abnormality of the preanesthetic voluntary cough and disease of the tracheobronchial tract:

1. A cough abnormality was almost always present when there was historical, physical or roentgenologic evidence of disease of the trachea or lower respiratory tract.

2. A cough abnormality was rarely found, and then only to a "mild" degree, in the absence of historical or other evidence for disease of the tracheobronchial tree.

3. A cough abnormality was usually attributable to excessive cigarette smoking or evident respiratory infection.

4. A cough abnormality was almost always recognized before operation in the patients who developed a cough or other respiratory complication within the first three days after gastric or biliary surgery.

5. A cough abnormality was usually absent before operation in the gastric or biliary patients who did not have a postoperative respiratory complication.

It may be fairly concluded from our data that an abnormality of the preanesthetic voluntary cough is a highly significant and very sensitive sign of tracheobronchial disease.

Discussion

The earliest and most constant evidence of tracheobronchial disease is hyperirritability, represented by the increased readiness, frequency and duration of a cough and the presence of secretions. Consequently it is to be expected, and this study so found, that an abnormality on induced coughing should be the earliest and most reliable sign of tracheobronchial disease. Those who might be skeptical of the clarity and frequency of the abnormal patterns of the induced cough on the basis of their experience with ambulatory patients seen in the clinic or in ward rounds should consider the differences in conditions preceding their examination and ours. We refer specifically to those factors described above which contribute to the retention of secretions in the respiratory tract. Secretions may lie in peripheral bronchioles without exciting a cough until they are brought into contact with the more sensitive mucosa at the entrance to a bronchus. An induced cough, like postural drainage, moves these bronchiolar secretions into positions where they may excite a spontaneous paroxysm of coughing, generate an audible "wetness" in the cough or reproduce an asthmatic wheeze. Surprisingly large volumes of sputum are obtained after a period of decreased ventilation and coughing caused by a surgical illness, bed confinement, drug-induced sleep and preanesthetic medication.[2-5] The use of the induced cough just before anesthesia as a *prophylactic* measure has been universally adopted for thoracic patients and is recommended by many authorities for all patients with known bronchitis.[6-8]

It is the purpose of this study, however, to direct attention to the value of the induced cough as a *diagnostic* method to be applied to all patients *just before anesthesia.* Experienced phthisiologists have always insisted on the patient's deliberate coughing during auscultation. "In the elicitation of râles produced by disease this (auscultation with a cough) is our most valuable procedure; therefore it should be employed as a part of every chest examination." [9] White,[8] Leithauser [11] and Alexander [7] have used the voluntary *diagnostic* cough *after operation* to elicit the presence of bronchial secretions as the first sign of an impending pulmonary complication. The extension of the use of the induced cough to the period *just before anesthesia* supplies a highly delicate yet significant method for the *diagnosis* of *preoperative* tracheobronchial disease.

Like those who have studied the problem of atelectasis complicating acute poliomyelitis [10] the anesthesiologist must learn to be suspicious of even the mildest form of irritation of the respiratory tract. Bronchial irritation is almost always associated with hypersecretion. Hypersecretion is the first and one of the most important of the factors which produce the important early postoperative respiratory complications.

Our experience has confirmed the frequently reported observation that many patients with postoperative atelectasis later admit having had a preoperative productive cough, whereas the preoperative study recorded no

evidence of any respiratory abnormality.[12-14] With our routine of preanesthetic induced coughing it has been easy to discover an obviously "wet" or paroxysmal cough in the absence of other evidence of bronchitis, to diagnose subacute or chronic bronchitis in patients who denied having a bronchial symptom until questioned closely for mild or transient cough and expectoration, particularly on arising from sleep.

It has always been difficult to account for the apparently sudden postoperative appearance of atelectasis with or without bronchitis in a patient without preoperative evidence of bronchitis. In the effort to explain this common discrepancy many theories have been proposed, attributing primary importance to mechanisms which, at best, are of secondary, minor or rare influence, e.g., neurogenic bronchospasm, rapid absorption of anesthetic atmospheres, decreased vital capacity, etc. Indeed, some students, like King [15] and Stoneburner and Finland,[16] have considered preoperative respiratory infections to play a minor rôle because they were noted in the hospital record in only 18.7 to 24 per cent of postoperative respiratory complications. Other investigators, however, depending more on their own examination of patients, have found a previous respiratory infection in a much greater proportion of patients with postoperative complications, e.g., 48 per cent of 60 cases of atelectasis, almost 100 per cent in cases with postoperative bronchitis,[17] and 60 per cent of 65 cases with postoperative pneumonia.[18] Gusterson,[19] in a study of combat troops who were smoking heavily and were exposed to inclement weather, found (*a*) 50 instances of preoperative respiratory abnormalities among 100 hernia patients, of whom 50 developed postoperative respiratory complications; and (*b*) 17 soldiers with preoperative respiratory abnormalities among 100 meniscectomies followed by 15 complications. Gusterson was impressed with the susceptibility of patients with a "smoker's cough"; he was therefore alert to detect the patient who denied having a cough and had a normal chest by physical and x-ray examination but was observed on the ward to have a morning cough and sputum. Harris, in a similar study of troops,[20] found that only those abdominal cases with a preoperative respiratory infection developed a postoperative chest complication.

Our experience substantiates Austrian's assertion [21] that, if we did not always find a preëxisting bronchitis in a patient who developed a postoperative atelectasis or pneumonia, it was because we did not look for it. Before we initiated the routine of preanesthetic induced coughing, we had 25 major respiratory complications after gastrectomy (atelectasis, pneumonia or asthma), with only four preceded by any evidence of a respiratory abnormality noted in the usual historical, physical, roentgenologic and preanesthetic data. The appearance of major postoperative respiratory complications did not then seem to be largely related to the preoperative status of the respiratory tract, and usually came as a surprise. We should have suspected, however, that we were overlooking many instances of preoperative

bronchitis in view of the fact that, in our gastrectomies during the same period, the 14 recorded instances of preoperative bronchitis were followed by 14 significant complications (one case of atelectasis, two of pneumonia, one of asthma and 10 of bronchitis).

The "wetness" of an induced cough is its most important characteristic in evaluating the gravity and the prognostic significance of an underlying bronchitis. This finding corresponds to the experience of Gray [22] and Seybold,[23] who seldom found postoperative atelectasis in patients with no sputum before pulmonary lobectomy, and with the conclusion of Mann [24] that lung lesions associated with a "dry" tracheobronchial tract, e.g., "dry" bronchiectasis, noncavitating tuberculosis, did not increase the incidence of postoperative respiratory complications.

The primary usefulness of the induced cough is that it serves as a screening device in the selection of those patients who require special attention to prevent postoperative atelectasis or pneumonia. It has been insufficiently appreciated that the patient with a mild bronchitis is prone to develop an extraordinary degree of bronchorrhea during and after operation, even after spinal, local or nitrous oxide anesthesia.[25] Aware of this fact, and aided by the screening value of the induced cough in the selection of patients for special prophylactic care, we have managed 200 gastrectomies and 400 cholecystectomies with striking success in reducing the incidence of respiratory complications. This report has just been published.[26]

Summary and Conclusions

We subjected 1,821 consecutive unselected patients and several hundred specially selected patients to voluntary forced coughing just before anesthesia. The abnormalities of the induced cough were classified and correlated with other evidence of disease of their respiratory tracts before operation.

An abnormality of the preanesthetic induced cough has been found to be the earliest significant sign of tracheobronchial disease.

The patient with a *normal* induced cough just before anesthesia rarely develops a serious respiratory complication during the first three postoperative days, even after a gastric or biliary operation, in the absence of contamination of the lower respiratory tract with gastric contents.

To avoid classifying an induced cough erroneously as normal, the observer must be experienced in the evaluation of the induced cough and in the consideration of the factors which interfere with the production of a vigorous cough effort.

The patient with an *abnormal* induced cough, particularly if it is "wet," is very likely to have a postoperative cough or more serious respiratory complication, especially after an upper abdominal operation.

The greatest value of the preanesthetic induced cough is in the diagnosis and selection of the patients who should receive special attention in order to prevent a major postoperative respiratory complication.

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UNUSUAL PHYSICAL FINDINGS IN PLEURAL EFFUSION: INTRATHORACIC MANOMETRIC STUDIES *

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The diagnosis of pleural effusion on physical examination has been based on the classic findings of absent tactile fremitus, dullness or flatness to percussion, and absent breath sounds. That the presence of increased breath sounds to the point of bronchial breathing and increased voice sounds can be associated with pleural effusions is not well known.

In an institution such as ours, with an active teaching program for four large medical schools, and interns and residents from many centers, it has been surprising to note the frequent lack of knowledge that pleural effusions can have protean findings. The fact that atypical findings may exist is not a new concept; it was described by Laennec in 1818.

Historical

Laennec,[1] in his "A Treatise on the Diseases of the Chest and on Mediate Auscultation," written in 1818, said, "When, however, the texture of the lungs becomes indurated or condensed from any cause, such as pleuritic effusion, . . . the vesicular respiration having then disappeared, or being much lessened, we can frequently perceive distinctly the bronchial respiration, not only in the large but even in the small ramifications of the bronchi. . . . The cause of this bronchial respiration appears to me very obvious; in fact, when the air is prevented from penetrating the cells, this is the only kind of respiration that can exist; and it is found to be louder and thereby most distinct in proportion as the lung is more condensed, and so becomes a better conductor of sound." He was also the first to describe and stress egophony as an important sign in pleural effusions.

Charles J. B. Williams [2] in 1834, in "A Rational Exposition of the Physical Signs of the Diseases of the Lungs and Pleura," explained these physical findings on a more physical basis, but in context agreed with Laennec.

The more modern texts used commonly in teaching today [3, 4, 5] make only passing reference to these "unusual" phenomena, the emphasis being placed on the more typical signs.

Deviations from the usual findings are quite apt to be confusing, as was demonstrated by two cases seen on a medical ward at about the same time.

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From the College of Medicine, University of Illinois, and Cook County Hospital.

Case Reports

Case 1. This 53 year old white female was admitted for the second time because of increasing ankle edema, dyspnea and orthopnea. She was known to have rheumatic heart disease. Physical examination revealed decreased tactile fremitus, amphoric breath sounds and whispered pectoriloquy over an area of dullness on the right below the fourth rib posteriorly. This was interpreted as pulmonary consolidation. However, because a thoracentesis had been done on her first admission, it was repeated, and yielded 1,800 c.c. of serous fluid with a specific gravity of 1.014.

The second case was strikingly similar.

Case 2. A 54 year old white female had complained of orthopnea and increasing dyspnea for two years and of ankle edema for two months. Six months earlier she had a left midhumeral amputation because of an embolus and resulting gangrene. Physical examination revealed an extremely dyspneic, slightly cyanotic white female. Her heart was fibrillating with an apical rate of 114. Examination of the chest revealed dullness of the left chest below the fifth rib posteriorly, with bronchophony and tubular breathing over the area. Because of the previous history of an embolus, the auricular fibrillation and these physical findings, a diagnosis of pulmonary infarction was made. However, thoracentesis yielded 1,200 c.c. of serosanguineous fluid with a specific gravity of 1.010. This was followed by immediate resolution of the physical findings.

Table I

No.	Name	Age	Sex	Etiology	Physical Findings	Pressure mm. of H_2O		Pleural Fluid	
						Ins.	Exp.	Amt.	Sp. Gr.
1	J. S.	54	F	Cardiac	"Unusual"	100	120	1,200	1.010
2	D. L.	27	F	Pneumonia	Usual	0	60	650	1.017
3	M. I.	42	F	Carcinoma	"Unusual"	330	350	3,550	1.007
4	E. B.	50	M	Carcinoma	"Unusual"	40	180	2,000	1.014
5	E. D. R.	42	F	Carcinoma	"Unusual"	50	120	3,000	1.010
6	M. F.	73	M	Cardiac	"Unusual"	100	140	3,000	1.012
7	P. Y.	53	F	Cardiac	Usual	0	110	1,200	1.012
8	J. W.	61	M	Cardiac	Usual	10	120	1,400	1.012
9	M. W.	21	F	Tbc.	Usual	0	40	550	1.018
10	J. W.	27	M	Tbc.	Usual	0	100	500	1.018
11	S. W.	70	F	Carcinoma	Usual	0	40	1,200	1.010
12	G. N.	47	F	Carcinoma	Usual	0	90	1,800	1.012
13	L. J.	55	M	Cardiac	"Unusual"	65	85	1,100	1.010
14	R. J.	73	M	Cardiac	"Unusual"	60	120	2,100	1.014
15	G. G.	64	M	Cardiac	Usual	—5	120	1,800	1.012
16	W. A.	58	M	Cardiac	Usual	—4	100	1,200	1.014
17	L. W.	44	F	Cardiac	"Unusual"	70	100	2,400	1.016

"Unusual": Findings of pulmonary compression with dullness-bronchophony and/or whispered pectoriloquy.
Usual: Absent or diminished breath sounds and dullness.

Several other cases have since come to our attention (table 1). Further study was undertaken to determine why a pleural effusion should yield findings resembling other disease entities. It was postulated that the fluid exerted pressure in these cases and caused parenchymal compression.

Physics

From the standpoint of the transmission of sound, the lung can be considered as composed of a system of tubes gradually decreasing in size, with the smallest tubes terminating in spongy tissue. The characteristic sounds, then, must be transmitted through this system and the chest wall to the examiner's ear.

The spoken sound originates in the larynx and is passively transmitted through the lung. Breath sounds are produced by air moving through the trachea and bronchi. Vesicular sounds are produced by air moving in and out of the alveoli, and this gives a more or less constant background murmur of sound.

In both health and disease, sounds from within the chest usually reach the chest surface with but a trifle of their former intensity, under even the most favorable conditions. Most of the loss is effected between media of different densities such as air and tissue, or air and fluid, and is due largely to the reflection of sounds. There is no appreciable loss between tissue and fluid. Air, fluid and tissue are each elastic media and good sound conductors. Fluid, however, will conduct sound better than air.[2,6]

Reflection of sound, with loss of intensity due to dispersion, is also caused by tense membranes containing air. This occurs in the normally expanded lung. As these tense membranes relax, sound loss is reduced. Sounds are also blocked by obstructions of an air passage, unless the area affected transmits sound directly across to the chest surface. This may be seen in an occlusion of a third division bronchus, with resultant segmental atelectasis. The same physical process would be present in a pneumonitis with consolidation, or in a pleural effusion externally compressing pulmonary parenchyma.

Increased sound transmission also occurs under a variety of conditions. A collapsed but aerated lung loses less sound conduction by reflection than does a normal lung. Solidified lung is a better conductor than a normally aerated lung, because it is of the same media and sound loss through it is practically negligible. However, some of the energy of sound is lost in passage from within the air tube to the solid lung. In a compressed lung, the vesicular sound being absent, with the resultant loss of this background murmur, bronchial sounds when present will appear more pronounced.[7,8]

The caliber of the bronchi is also important in sound transmission, because when sound reaches bronchi of 5 mm. or less it is reduced in intensity because of friction. Nothing is conducted in tubes of 3 mm. or less. For typical breath sounds to be heard, there must be good conduction between the chest wall and bronchi of greater than 3 mm. bore. The sound will be of greater intensity if conducted from bronchi of greater size because less sound energy has been lost along the tubes. Sounds are fairly distinct, and pectoriloquy is produced when bronchi of 5 to 6 mm. are reached.[9,10]

It has been shown by anatomic dissection [11] that bronchi of 3 mm. bore

are about 3 cm. inward from the pleura in the upper portion of the lung; 3.5 to 5 cm. inward in the basal and axillary portions, and 1.2 cm. inward near the vertebral column. Less compression then will be necessary near the vertebral column to reach bronchi of significant size.

Fluid between the lung and the chest wall is of itself a good conductor. In contact with the chest wall, however, it lessens or abolishes the normal tissue vibratability and causes some sound loss. Sound, once transmitted to the fluid, is carried to the chest wall unaltered because there is no loss due to sound reflection in the fluid.

Manometric Studies

Because of the above discussion and our findings of pleural effusion in those findings considered "unusual," we decided to determine by manometric studies whether the fluid was under pressure and causing parenchymal compression.

The lung normally floats in a potential pleural space having a negative pressure. Fluid introduced into this potential space will be subject to certain forces, as it would be in any other closed space. Gravity will tend to pull the fluid to the bottom of the space and capillary action will pull some of the fluid up the chest wall. The fluid, if under pressure, will exert pressure in all directions equally, in accordance with Pascal's law. The amount of compression or displacement of the lung depends on the external force, pressure and amount of fluid. There are also many variable factors which resist displacements such as fibrosis and congestion within the lung, fixed mediastinum and adhesions preventing movement of the involved lung.

Manometric readings were taken to determine the pressure contained in the fluid in effusions with usual and "unusual" findings. A spinal manometer connected to a three-way valve and a thoracentesis needle was used (figure 1, A). Since this could not demonstrate negative pressures, the "U" manometer of a pneumothorax apparatus was used in certain cases. Because the height in the fluid at which the needle was inserted could not be accurately predetermined, readings were taken at two levels in the effusion, one 10 cm. above the other, and were found to be approximately equal (cases 4 and 11). In an effusion, then, the fluid is in accord with Pascal's law, which states that pressure in a fluid is transmitted equally in all directions. In an enclosed system, such as would be had in the pleural space, the pressure is transmitted to lung, chest wall and manometer equally, regardless of where the manometer needle is inserted.

The level of the manometer fluid will not be the same as that of the effusion, as would be expected in an open system (figure 1, B). In such a system, the only force would be that of gravity, while in the pleural space the fluid is under pressure and transmits that pressure to the manometer.

Pressure readings taken above the fluid, at the vertebral border of the scapula, demonstrated that normal negative pleural pressure was maintained

at that level (cases 15 and 16). This had earlier been demonstrated in dogs by Hewlett [12] with artificially induced hydrothorax.

The results of these manometric studies (table 1) demonstrated that in those effusions with "unusual" findings the fluid was under positive pressure through all phases of the respiratory cycle. It is not the height of pressure that is important but only that it is elevated or positive. In this series of 17 cases eight had "unusual" findings on physical examination, and all eight had pressures that were positive throughout the cycle. All of these were in effusions due to cardiac decompensations (cases 1, 6, 13, 14, and 17) or carcinoma (cases 3, 4 and 5). This is probably because these effusions are more likely to have a fairly rapid onset and to contain more fluid. An

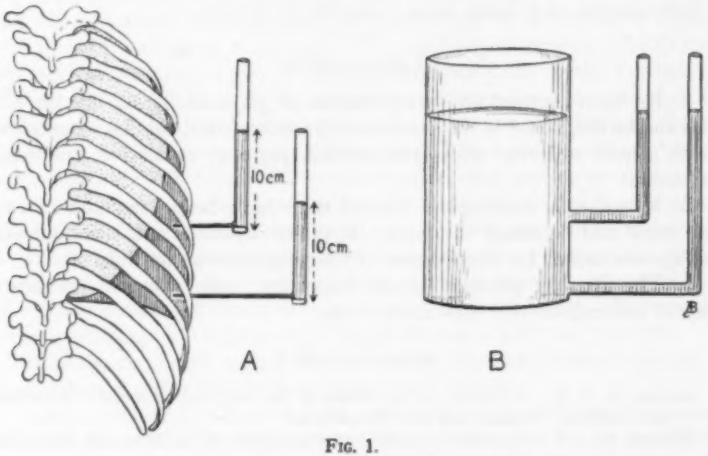

FIG. 1.

effusion due to an inflammatory process, however, could probably achieve the same results if acute and massive enough.

All the remaining patients (cases 2, 7, 8, 9, 10, 11, 12, 15 and 16) had usual findings and showed negative pressure in the inspiratory phase. This was demonstrated by absence of fluid in the spinal manometer or negative reading on the "U" tube of the pneumothorax apparatus.

It is also of interest to note that effusions that had "unusual" findings but did not appear to be "massive" on x-rays or percussion contained more fluid than an effusion of equal height with the usual findings. This is because the thickness of the fluid is difficult to determine by either x-ray or percussion, and the total fluid will depend on this dimension. A thick effusion will be more likely to cause compression and yield bronchophony and tubular breathing than will an equally high but thin effusion.

Summary

Manometric studies were performed on 17 cases of pleural effusion to determine the pressure contained in the fluid. An attempt was made to correlate the pressures with the physical findings. In all eight of those with constant positive pressures throughout all phases of the respiratory cycle, "unusual" findings of bronchophony, tubular or amphoric breath sounds and even whispered pectoriloquy were noted. The etiology of all the effusions in this series was either cardiac decompensation or carcinoma. However, this is probably because these are more apt to be larger effusions which have developed rapidly. Absolute pressure does not appear to be significant, but only that some degree of positive pressure is produced and held. This pressure must be sufficient to compress parenchymal tissue down to bronchi of sufficient size to produce these auscultatory findings.

Conclusions

1. By more meticulous interpretation of physical signs, pleural effusions can be diagnosed in the presence of bronchophony, tubular or amphoric breath sounds and even whispered pectoriloquy over an area of dullness to percussion.

2. Manometric readings of pleural fluid have been presented in cases with usual and "unusual" findings. It is demonstrated that the "unusual" findings are caused by compression of lung parenchyma by fluid.

3. The absolute pressure is not important; only that the pressure is positive throughout the respiratory cycle.

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RADIOACTIVE IODINE IN THE TREATMENT OF HYPERTHYROIDISM *

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Radioactive iodine has been used in the treatment of hyperthyroidism for over 10 years and is much more popular today than ever before. Of the 12 isotopes of iodine known, only I^{131} is now used in thyroid disease.

There are many fortunate circumstances which make I^{131} particularly useful, especially in Graves' disease. I should like to recall to your minds what some of these characteristics are, and to enumerate seven of them.

First, although in essentials the effects are the same as from x-ray or radium, with them the radiation dose to the thyroid is limited to approximately 2,000 roentgens, while with I^{131} in diffuse goiter over 10,000 roentgen equivalents (r.e.p.) can be placed conveniently inside the thyroid.

Second, the uptake is high in hyperthyroidism when it is needed, and is low enough, when thyroid function is normal, so that it is difficult to cause hypothyroidism if a normal gland is treated. The thyroid in Graves' disease can concentrate I^{131} about 10,000 times more than any other tissue.

Third, because about 85 per cent of the radioactivity in I^{131} is beta rays, which travel 2 mm. or less, tissues adjacent to the thyroid are not damaged.

Fourth, the half-life of eight days means that 99 per cent of the original strength is dissipated in 52 days. For this reason it lasts long enough to be effective and disappears soon enough that an error in dosage does not cause excessive damage if too large or, if too small, can readily be corrected.

Fifth, in the doses used it has caused no renal or bladder damage, no amenorrhea, no infertility and no parathyroid damage.

Sixth, although I^{131} is not suitable treatment for hyperthyroidism in pregnancy, if given in early pregnancy the fetus is protected by the inability of its thyroid to concentrate radioactivity until after the third month.[1]

Seventh, I^{131} can be used in testing the thyroid function because the activity is carried by a dose of chemical iodine too small to affect the normal physiology of the gland. Doses in common use are on the order of one thousandth part of a microgram or, say, less than a fifty thousandth of the normal daily requirement.

The only obstacles to the use of I^{131} in Graves' disease are the facts that it is not generally available and that its effects may be blocked by iodine given in various ways, as in iodine medication, in radio-opaque materials or, more recently, in iodinated thioureas. In nodular goiter there have been, up to the present time, two other factors which may be considered disadvantages

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From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

to this type of treatment: The tendency to slow response, and the failure to remove the nodules completely.

It has been feared by some that this treatment might eventually lead to carcinoma of the thyroid in some patients. During the past decade of its use, however, there has been no evidence to suggest that this has occurred.

Radioactive iodine is received by air from Oak Ridge at weekly or fortnightly intervals. It is restandardized and diluted in colored water to a strength of 4.0 mc. per 1.0 c.c.

I^{131} IN DIAGNOSIS

I^{131} has supplemented the means of diagnosis of hyperthyroidism in several ways. The measurement of I^{131} uptake by the thyroid is almost routine practice wherever the isotope is used. It has considerable diagnostic value if properly interpreted. It is much less valuable in nodular goiter than in Graves' disease.

Test doses originally in the range of 100 to 200 microcuries can now, with the aid of improved equipment, be reduced to as little as 10 microcuries in most tests if this is considered desirable.

In our hands, normal 24 hour uptake values lie between 15 and 45 per cent of the dose given; 45 per cent to 60 per cent are borderline, while levels below 15 or above 60 are abnormal. In interpreting such tests it should be kept clearly in mind that we are not measuring hyperthyroidism as such, but only the avidity of the thyroid for iodine. This may be altered by factors other than hyperthyroidism, such as iodine starvation, as Stanbury [2] has shown, or the uptake may be blocked by larger than normal amounts of iodine in the thyroid, as already mentioned. It may be temporarily increased by an increase in effects from thyrotropic hormone, as experienced subsequent to the injection of this hormone, or when anti-thyroid drugs increase its physiologic production. Uptake levels are decreased by suppression of thyrotropic hormone, as after thyroid feeding or in patients with certain pituitary tumors. Even under well controlled conditions it is often difficult to recognize a close correlation between the percentage of I^{131} uptake and the degree of hyperthyroidism present.

Urinary excretion of I^{131} is easily measured but not so readily accomplished as uptakes. In general it accounts for most of the radioactivity not localized in the thyroid—that is, if the uptake approaches 75 per cent, the excretion would be expected to approximate 20 or 25 per cent. In practice this seldom adds much to the certainty of diagnosis of Graves' disease, but it may be of great value if the thyroid is unusually large, unusually placed, or if one is dealing with metastases.

Radioactive protein-bound iodine can be measured in the blood serum. Dwight Clark [3] has developed a method of comparison of the total radioactivity of the serum compared to the radioactivity of the precipitable protein

which contains thyroid hormone. This gives the "conversion index," which promises to be a useful and accurate test in diagnosis of doubtful cases.

I^{131} in Hyperthyroidism of Nodular Goiter

In multinodular goiter the consensus (with which we agree) is that surgery is usually the treatment of choice. There is a great discrepancy of opinion regarding the risk of cancer in multinodular goiter. However, most investigators believe that the risk is sufficiently great to warrant advising the patient that such masses should be removed, even though it is clearly recognized that in most patients some nodules remain after surgery and that cancer has been known to arise in such remaining nodules.

If surgery for any reason seems unacceptable in treatment for nodular goiter, the hyperthyroidism which exists can be controlled with radioactive iodine.

When I^{131} therapy is being considered it is important to make a clear differentiation between the hyperthyroidism of nodular goiter and that of Graves' disease, because these two types of hyperthyroidism respond differently in several important respects:

1. The dose required for control is larger in the nodular goiter.
2. The rate of improvement is slower.
3. Larger doses may be given with impunity because post-treatment myxedema, to my knowledge, has never been observed in this condition.

Our experience with the I^{131} treatment of hyperthyroidism of nodular goiter is based on the study of 102 patients. In them the dose requirements for control varied widely. Three patients required only 7 mc., and the high limits were 90 and 95 mc. in two. In general the large goiters required large doses. The average dose for the whole group was 34 mc., as compared to 12 mc. for Graves' disease.

The other difference which was mentioned was the time factor, namely, that most patients with Graves' disease are controlled in two to four months, while those with nodular goiter, by the methods and doses we have used, take an average of six and one-half months. It is often important in nodular goiter to eliminate the existing hyperthyroidism quickly because of cardiac failure, and this has been attempted recently by giving amounts as large as 50 mc. at one dose. The first few attempts of this have proved successful, the hyperthyroidism disappearing in two or three months after a single dose.

I^{131} in Graves' Disease

Radioactive iodine has not only been most outstanding in the therapy of the hyperthyroidism of Graves' disease but has been the most successful isotope in medicine.

It should be reëmphasized that it is important for the clinician to be certain whether he is dealing with nodular goiter or Graves' disease. This is the first step in the estimation of the proper dose to be given.

Selection of Patients

The most evident indication for I^{131} therapy is in recurrent hyperthyroidism after surgery. It is also clearly indicated in patients who are cardiac cripples or who are aged, and is also frequently used in patients who have had a recurrence after antithyroid drugs. Because in the minds of some there is a remaining fear of cancer, such therapy seems more applicable in instances where the patients are over 40 years of age, but the age rule has become more flexible as the years have passed.

The Dose

No experienced surgeon would guarantee a cure of hyperthyroidism in each of 100 patients treated; similarly, there is no method known by which the completely effective dose of I^{131} can always be calculated. The fundamental reason is that the cause of the disease is unknown and cannot be properly evaluated or quantitatively controlled.

Methods of calculation of dosage are currently based on the weight of the gland, as established roughly by palpation of the neck, and the percentage uptake of I^{131} by the gland. The prescribed dose usually lies between 100 and 200 microcuries per gram of thyroid. By such methods the cures on the one hand and the number of patients with hypothyroidism on the other still fall much wider of the mark than is desirable.

Doses as small as 3 mc. have been known to cause hypothyroidism in some patients, and 93 mc. have failed to produce complete control in others.

One method, in use by us, is essentially empirical. As an example, it has been found that for a gland of an estimated weight of 60 gm. the average total curative dosage has been approximately 10 mc. Assuming an in vivo uptake of 60 per cent, the effective dosage would theoretically be 100 mc./gm.

Thus, considering an effective dose per gram of tissue, the administered dosage requirements vary according to the size of the gland and its avidity for iodine. Since in Graves' disease the avidity for iodine is greater when the hyperthyroidism is more intense, the gland tends, within limits, to retain automatically the amount of I^{131} needed.

To avoid all unnecessary hypothyroidism, two-thirds of any average curative dose has been given. This has resulted in control of 75 per cent of the patients by one dose, 15 per cent by two doses, and 10 per cent by three or more doses.

This method is being compared with one in which an uptake measurement of a tracer dose is used in conjunction with gland size to calculate the actual I^{131} energy deposited in the thyroid, and to determine if this produces

in the patients more cures in one dose with no greater proportion of hypothyroidism.

If the patient has been pretreated with iodine in any form intentionally or inadvertently and the uptake is low, treatment with I^{131} is postponed and propyl or methyl thiouracil or mercaptoimidazole may be given for a month to maintain control; two or three days after withdrawal of the antithyroid drug, I^{131} can be used.

All patients are asked to return two months after the first treatment. The general rule followed is that if no improvement has occurred the original dose is repeated. If improvement represents an approach halfway to normal, half the original dose is given; if the patient has come to a point of improvement where the basal metabolic rate is less than plus 20 per cent, and there is reason to suppose that normality may be reached in one or two more months with changes occurring at the same rate, then no more treatment is given until another two months have passed.

Results

We have now treated 642 patients with Graves' disease and the results are consistently excellent.

There seems to be almost no disadvantage to the method. To mention those which are present, we may say that it has the same inherent disadvantage as other methods: it does not attack the disease at its source. It causes some myxedema, but not more than follows thyroid surgery. This is a minor complication at any time and, in fact, even appears to be the inevitable accompaniment of a cure in some cases. There is the slight disadvantage that complete control of the hyperthyroidism may be slower than that following surgery. This is usually inconsequential, since the patient is almost always able to continue his normal activities while the hyperthyroidism is diminishing.

One other disadvantage, in common with surgery, is that the gland is not intact, and here antithyroid drugs have an advantage over both other forms of treatment.

Hypothyroidism has occurred in approximately 10 per cent of patients with Graves' disease. This is often transient.

Of the hundreds of patients treated, the only complication other than hypothyroidism was near-crisis, which required concentrated treatment in one patient who had received a 25 mc. dose. This we believe can now be avoided if I^{127} (ordinary iodine) is always given beginning two days after the I^{131}. This was not done in the patient mentioned.

The situation remains essentially the same as when our first 203 cases were reviewed. The outstanding facts then were that 98 per cent of the patients were free of hyperthyroidism six months after treatment. Failure has been experienced in only one patient, who was operated on after 93 mc.

and a year of treatment. Therapy was abandoned in two children in favor of surgery rather than persist in repeated doses of I^{131}. Exophthalmos apparently behaves the same after I^{131} as after other forms of treatment; that is, it frequently becomes a little worse at first, sometimes a little better. Eventually it tends to improve in most patients, but occasionally it may become extremely severe. Recurrences have been observed in about 2 per cent of the patients in whom the basal metabolic rate has reached normal and later risen to hyperthyroid levels. This may be seen anywhere from 20 to 50 weeks after treatment, in our experience to date. Retreatment seems just as effective under these circumstances as it was at first.

Of the many advantages to the I^{131} treatment of Graves' disease we may list:

1. No deaths.
2. No vocal cord paralysis.
3. No chronic tetany.
4. Almost 100 per cent complete control.
5. Thyroid size reduced, usually to normal.
6. No discomfort.
7. No time loss; no loss of income.
8. No hospitalization.
9. Hyperthyroidism no more frequent than after surgery.
10. Fewer recurrences than in other forms of treatment.
11. Recurrences easily and successfully treated by I^{131}.
12. Cheapest form of treatment.

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PROGNOSIS IN SOME PSYCHOSOMATIC DISEASES*

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PHYSICIANS are constantly searching for means to improve their ability to "foretell the cause and termination of a disease" and also "the outlook afforded by this" knowledge. The skills and concepts of John Hunter, W. W. Gull, James MacKenzie and William Osler are being broadened and deepened by the new facts which are crowding upon us from our daily practice. This is especially true for those "successes" which leave something to be desired. A few examples will illustrate how we are compelled to enlarge our working concepts of physiology and of a patient as an organism dependent upon his social as well as his physiologic matrix. I have no answers, but suggest familiar questions.

Among our more recent patients we have seen a 35 year old married woman (Mrs. B.), who recovered from a peptic ulcer only to develop a mucous colitis, which is now in abeyance, but the patient shows new mild paranoid patterns. Another patient (J. R.), with catatonic schizophrenia, has severe psoriasis when his mental symptoms improve and vice versa. Three other patients (H. S., J. K. and E. G.) with psoriasis also seem to have exacerbations of their skin disorders when their mental conditions improve. One of them (E. G.) also has increased gastrointestinal discomfort with improvement in the skin condition.

What are the facts about the incidence of psychosomatic disorders in psychoses? Only 21 (2.1 per cent) of our 965 psychotic patients have shown concomitant psychosomatic disorders, but it is apparent that some of these disorders are altered by the course of the psychosis or the therapeutic process. At the Boston State Hospital, Swartz and Semrad[6] discovered that their incidence of psychosomatic disorders in psychotic patients was 3.4 per cent (of 578 patients), as compared to 4.5 per cent (of 314 patients) in the nonpsychotic group. They describe three categories of relationships. In category 1, as in the examples cited, there seemed to be an inverse relationship between the psychosis and the physical disorder. These included headaches, hypertension, dermatitis, asthma and peptic ulcer.

Category 2 included patients whose physical disorders were apparently unaffected by the psychoses. These disorders were headaches, hypertension, dermatitis and mucous colitis. Category 3 included two cases whose psychosomatic disorders (a peptic ulcer in a 43 year old man and convulsive seizures in a 27 year old woman) were apparently aggravated by either the psychosis or the therapy.

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These patients call attention to the need for larger series, since in our series at the Western Psychiatric Institute there were only five cases of peptic ulcer (0.5 per cent), and to the best of our knowledge they were not aggravated by the psychosis. The woman patient first cited highlights the observation that relatively few functional psychoses have convulsive seizures, giving rise to the legends that seizures and psychoses are incompatible. This notion, to some extent, prompted Sakel and Meduna to use insulin and metrazol as therapeutic agents in the so-called functional psychoses.

A brief note is in order to emphasize that the number of cases under review is too small for generalizations; that the problems of causality differ from those of concomitance, as described long ago by David Hume, and from those of meaning, as described by J. C. Whitehorn; and that the attractive theory that psychosomatic disorders are in some way or to some extent a "defense" or a barrier against a psychotic pattern needs much more validation. We are becoming accustomed to the concept of a psychosomatic affliction as a partial manifestation of maladaptation to life stresses by the human organism. Since this adaptation often permits the person to carry on his job and domestic duties in conventional ways, we tend to think of these patterns as relatively more mature or successful ego organizations.

We also infer that some stresses will cause psychotic, i.e., inferior adaptive patterns, even though the chain of development is not understood either psychologically or physically. Headaches, seizures or increased blood pressure, for example, may be expressions of repressed rage in psychotics and non-psychotics alike, but it may be that some psychosomatic disorders are, as it were, either a defense against a psychotic reaction or an equivalent to it.

With these cautions in mind, we can examine the findings of Ross, Hay and McDowell [5] on 1,600 patients in a Canadian mental hospital. Peptic ulcers were found in 0.6 per cent of their admissions, a low incidence as compared to control groups. Bronchial asthma was found in only 0.8 per cent, which agrees with other studies and contrasts with control studies of 1.5 to 2.0 per cent for the United States, as reported by Balyeat. Five (or 0.5 per cent) of our cases had some asthma. Ross had 18 diabetic patients (or 1.1 per cent). We had two (or 0.4 per cent), which may not be significantly different from the general population.

Rheumatoid arthritis occurred in only 0.25 per cent of Ross's cases and 0.13 per cent of 15,196 psychotics in Gregg's series, and in 0.4 per cent of ours at Western Psychiatric Institute. This contrasts with a reported incidence 17 times greater in the general population of Massachusetts.

Hyperthyroidism was found in only 1.0 per cent which is not remarkably different from other similar studies or control studies. Dr. J. H. Means states that accurate information is not available. We had only one case and one with a previous thyroidectomy.

Ross and his colleagues point out that these observations favor the hypo-

theses that physical factors are most important in diabetes mellitus and bronchial asthma, or that the "relevant emotional factors are at a psychotic level." On the other hand, peptic ulcer might be better understood as a "vegetative neurosis," and rheumatoid arthritis, which seems rare among psychotics, as a "motor neurosis."

With these facts as a background, we can examine the change in psychologic status in patients under therapy with cortisone and ACTH.[2] Clark et al. report a series of four minor and six major cases of mental disturbance occurring in the course of hormonal therapy. "Complete recovery occurred spontaneously in all cases," usually following withdrawal of the drug, and upon applying only supportive measures. "The pattern of recovery in the prolonged cases showed the occurrence of lucid intervals of gradually increasing frequency and duration until a normal mental state was consistently present." Careful review of the psychiatric history and the mental status did not reveal significant symptoms or patterns which would signal to the physician that the patient was susceptible to a mental disturbance. There was no indication of other factors, such as other drugs or physical disease, which might cause a toxic psychosis. Nine of the cases had some type of rheumatoid arthritis, although five also had some other complication, such as Reiter's syndrome, peptic ulcer, iritis and psoriasis. The tenth case had severe disseminated lupus erythematosus complicated by convulsive seizures, although there was no history of epilepsy. It is notable that these patients showed a wide variety of common psychotic behavior and that there were no distinctive patterns. The authors, recognizing the possible misinterpretation from their descriptive material, protect themselves by stating, "Whenever recourse is made to psychological abstractions, the latter should be regarded as descriptively analogous to, rather than identical with, corresponding phenomena in previously described psychiatric illness." The distinction is well worth making, just as we distinguish between waking thoughts and acts and those dreams which occur during the complex process of sleep. This does not mean we need to forego the risks involved in interpreting some of the behavior if its meaning gives us better understanding of the behavior, and even permits better care of the patient during this period of acute stress. The mild elation or euphoria seen so often is commonly interpreted as the expression of relief from discomfort and pain. However, the frank psychotic pictures of mania, depressions and paranoid states, with more or less tension, irritability, querulousness, hostility, aggressiveness, withdrawal are not so easily understood. There are other physical factors also to be considered, such as the electroencephalographic changes (Hoefer and Gloser, 1950). These changes in Addison's disease can be corrected with the giving of cortisone, and in the adrenalectomized animal with ◇ 5 pregnenalone (Hoagland). There are probably personality changes in both hypoadrenal and hyperadrenal cortical functions (G. Thorn).

On the other hand, some authors believe that the psychotic behavior can also be understood. Rome and Braceland state in an early paper:

"From these preliminary observations we have been led to the assumption that the sudden and profound variation in the *milieu interieur* which so markedly affects the patient's metabolic homeostasis is similarly disruptive of his psychologic adaptation. The variety and degree of this disruption seem to be the resultant of many vectors. Most important among those presently identified are the organization of the patient's personality, the psychologic meaning of the patient's disease to him, the emotional investment he has in his physical person, and his specific symptoms and the significance of the secondary gains which have accrued to him. Collectively these institute a major stress as taxing of his psychologic adaptation as any external environmental stress would be to an equally vulnerable person." [4a, 4b] This thesis is elaborated by them in a paper read at the Association for Research in Nervous and Mental Diseases in December, 1951, to be published in the annual yearbook.[4, 4a] It is worth noting that Borman and Schmallenberg [1] report a suicide following cortisone treatment.

Let us return to our case, Mrs. B., who developed in turn peptic ulcer, mucous colitis and paranoid trends. The latter succession is not uncommon and will be reported in detail in the near future by several investigators independently. Here we face again the problem of a possible connection between a series of events in a patient's life called by physicians "peptic ulcer" being succeeded by another series called "colitis" and again by another called a "paranoid state." In 1948, Dr. Karl Menninger [3] read a paper to this group emphasizing the same thesis, namely, that neither the peptic ulcer nor the colitis and associated depressive or paranoid states are in themselves the disease. The disease is a defective total life adjustment. He told of a young banker with a peptic ulcer who made an uneventful recovery following a gastrectomy, but became depressed, did not return to work and committed suicide before he could be sent to a sanatorium.

This example could be multiplied for many procedures, including gastrectomies, vagotomies, sympathectomies, etc. While mild depressions are common enough following many surgical procedures, there are also a sufficient number of suicidal depressions (occasionally successful), alcoholic and drug addiction patterns, and a host of other kinds of psychiatric disorders not related to the basic surgery to make us wary. These complications are so severe that they deserve careful attention from all physicians. It may be possible, at least in some cases, to detect those patients whose underlying personality patterns betray their underlying disorders so that they can be treated appropriately before being subjected to major stresses such as ACTH or surgery. Prognostic signs will be developed as we learn where to look for them.

In this connection, it is interesting to note that similar mental disturbances follow the use of Antabuse. There is no question that if a patient will

accept the discipline of taking the drug (and many do not), he can be "dried out" and often will stay so for long periods. However, in these "dry" periods the patient may show depressive states; some commit suicide. Hostile aggressive reactions, complaining, apathy and projections are not uncommon. It is well known that a helpful family setting will often assist a patient to adjust, but the crucial factors are not always easy to recognize, for the domestic relations may paradoxically become worse. I know of a case where the wife would have a severe weeping dermatitis when her husband was sober under treatment, and would recover when her husband returned to drinking. Dr. Karl Menninger mentioned the young wife whose dysmenorrhea disappears when her husband is drunk. We must again ask ourselves how we can improve our predictions about a patient so that he will be given more comprehensive treatment for his real problem: his maladaptation to his fellow men.

It is probable that the organization Alcoholics Anonymous is able to help 40 per cent or more of alcoholic patients by means of their well worked out system. It seems to me that they are able to provide much appropriate emotional support in a stable manner which deserves close study. They substitute some medium, an intake of forces, which is more than an adequate substitute for the drug effects which are taken away. Here we have a chance to compare the methods of Antabuse and Alcoholics Anonymous, and to try to apply this to other disordered biological systems. Most authors state that psychotherapy is a necessary adjunct to the use of Antabuse, but the nature of these complex activities and the quality of the support from the family can probably be described sufficiently accurately to make comparisons possible.

The familiar request for more appropriate follow-up care is also well illustrated by Uniker, who asks, "What comes after Dilantin?" [7] He calls attention again to the concept that the patient has the same personality even though the attacks have ceased, and that the advantages of the drug may be somewhat nullified by the emergence of new patterns of a neurotic or even psychotic nature.

Similar cautions can be ventured in the treatment of those severe cases of obesity in which the need to eat or drink large amounts has all the force of an addiction. The balance of intake and output cannot be disturbed harshly, or with impunity, unless the organism is given adequate support by the environment. To a less dramatic extent, this is also seen in the weight-reducing régimes for middle aged men and women. Some of them do not adapt well to the poverty of intake forced upon them by the new diet. The loss of the cocktail hour may occasion more conflict than the patient can handle. The physician's prognostic acumen will be sharpened if he can gauge the emotional meaning of the intake and provide means to reduce both the inner and outer tensions of the patient's life and can also, perhaps, encourage better substitute activities.

The need for prognostic judgment is highly acute in deciding upon electroshock therapy or some variety of psychosurgery. Repeatedly we have seen failures of adaptation or even deterioration in behavior when the patient's needs are not met following the physical intervention.[8]

In the absence of a really good model for the workings of the mind, one which permits more accurate quantitative experimentation, we must use the best devices we have to explain the wide series of events briefly discussed here. Among the hypotheses which may eventually prove most useful seem to be those of dynamic psychiatry in which human behavior is regarded as meaningful, i.e., it can be understood by common sense. Usually the meaning can be detected in the purposes served by the series of events we call a disease. These purposes are sometimes obscure because they may be rooted in repressed emotions which continue to exert a powerful influence upon overt behavior. That there are different types of learning, including those outside the field of awareness, is being shown experimentally in both men and animals. Only as we school ourselves to observe these patterns will we become skilled in predicting the outcome of a disease, and also "the outlook afforded by this."

While this may seem a big chore, even intimidating at times, we can take heart at the wisdom and courage expressed by Sir W. W. Gull in the Harveian Oration (1870), in which he declared the faith that all aspects of biological man's behavior was the proper concern of the physician. We have more complex problems, perhaps, than our grandfathers had, but we have more means with which to meet them.

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THE NEUROSURGICAL TREATMENT OF SPONTANEOUS INTRACEREBRAL HEMORRHAGE SIMULATING THE COMMON STROKE*

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THE appalling mortality from massive hemorrhage into the cerebrum is common knowledge. The Metropolitan Life Insurance Company in 1946 listed this condition as fourth in the cause of death.[1]

This fact has encouraged neurosurgeons to attempt removal of the clot and control of hemorrhage in selected cases. The results in small series as reported by various neurosurgeons have been encouraging.[2-17] This has stimulated the author to operate on a group of carefully selected cases, and then gradually to extend the procedure in some instances to those with grave prognosis with the hope that life might be saved.

The first step in evaluating these cases has been to differentiate intracerebral hemorrhage from cerebral thrombosis or embolism, because the use of stellate blocks and/or anticoagulants, advocated by some in the treatment of cerebral thrombosis, could be disastrous if used in intracranial hemorrhage. The diagnosis of cerebral embolism is usually not difficult.

I have attempted to show the differential points between intracerebral hemorrhage and cerebral thrombosis in table 1.

Once a diagnosis of hemorrhage is made one must decide whether or not a cerebral aneurysm or vascular malformation is the cause of the bleeding. Usually these conditions are more frequent in those below 50 years of age and in those who have no history or evidence of hypertension. The frequency of congenital saccular aneurysms as a cause for intracerebral hemorrhage can be obtained from Zimmerman's studies. He dissected the brains of 107 patients who died from spontaneous intracerebral hemorrhage without operation. Congenital aneurysms were found in only 14 of the cases (13 per cent).[18] An analysis of 134 cases of spontaneous intracerebral hemorrhage subjected to operation (including the author's 29 cases) reveals that at operation only five aneurysms were definitely found, approximately 4 per cent; however, it should be emphasized that cerebral angiography was done in only a few of these cases.

The following are the author's indications for cerebral angiography:

1. If the clinical data suggest aneurysm rather than hypertension as the etiology.

2. If x-rays of the skull do not show a calcified pineal gland.

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3. If it is impossible to differentiate between thrombosis and hemorrhage, and the patient is showing progression in symptoms.

4. If the patient is showing rapid progression in symptoms and signs, and accurate localization cannot be made by neurological examinations.

TABLE I

Differential Diagnosis between Spontaneous Intracerebral Hemorrhage and Cerebral Thrombosis

	Hemorrhage	Thrombosis
Mode of onset	Sudden	Usually gradual
Progression	Usually rapid	Often gradual
Headache	Severe and usually on side of hemorrhage	Mild or absent, severe only if edema is present
State of consciousness	Drowsy to coma	Usually not impaired unless edema is present
Blood pressure	Hypertension frequent (50%)	Hypertension less frequent (25%)
Eye grounds		
Retina	May show hemorrhage	No hemorrhage
Vessels	Hypertensive changes	Arteriosclerotic changes
Disc	Normal, choke later	Normal
Spinal fluid		
Pressure	Elevated 79%	Normal
Color	Bloody 65%	Normal
Skull roentgenograms	Pineal gland shifted to one side by clot	No shift unless edema is present
Cerebral arteriogram	Displacement of arteries Aneurysm may be visualized	Occlusions of artery in cerebrum or in neck

The final problem is whether intracranial intervention is indicated. There are cases of intracerebral hemorrhage in which the bleeding stops spontaneously and partial or nearly complete recovery occurs.

The author considers the following indications for surgical intervention:

A. Symptoms and signs of a *progressive* increase in intracranial pressure:

1. Loss of consciousness levels progressing to stupor or coma.
2. Stertorous respirations.
3. Progressive slowing of the pulse rate (below 60) and respirations (below 16).
4. Increase in spinal fluid pressure (above 160 mm. of water).
5. Choked discs, if the symptoms persist for days.

B. Any neurologic signs of focal involvement of the brain showing progression:

1. Aphasia (sensory or motor and usually early, before stupor or coma).
2. Visual field cut (early).
3. Hemiplegia or hemianesthesia.
4. Fixed dilated pupil on one side.
5. Unilateral convulsions.

C. Roentgenograms revealing a shift of the pineal gland away from the suspected cerebral hemisphere.

D. Arteriogram showing aneurysm or space-taking clot.

Analysis of the Author's Cases

Cases of spontaneous subarachnoid hemorrhage due to intracranial aneurysm but with no evidence of bleeding into the cerebrum are not included in this presentation.

This report deals with 29 consecutive patients operated upon by the writer * for spontaneous intracerebral hemorrhage. (Twenty-three cases were reported previously, before the Section on Neurology at the convention of the American Medical Association in June, 1951.) Twenty-four patients had hemorrhage into the various lobes of the cerebrum, three had hemorrhage into the subdural space, and two had hemorrhage into a highly vascular tumor.

Seventy-five per cent of the patients were between 40 and 66 years of age. Fifty-two per cent had a history of known hypertension before onset of the cerebral accident. Headache was an early symptom in 72 per cent of the patients, and when it was unilateral it always corresponded to the side of the hemorrhage.

In every case the neurologic signs permitted a correct localization to the involved hemisphere. Twenty-three patients had a paralysis of one side of the body, and in five partial to complete decerebrate rigidity was present.

The spinal fluid was bloody in 65 per cent of the cases and was above normal pressure in 79 per cent.

An exploratory craniotomy was done in 18 cases and an enlarged trephine in 11.

Liquid blood only was aspirated in five cases, and large hematomas, frequently with some liquid blood, were found in the remaining 24.

In four cases the hemorrhage was caused by a rupture of an artery with no visible aneurysm. In one case an aneurysm of the right middle cerebral artery was found.

A chorioepithelioma and a malignant melanoma were the cause of hemorrhage in two cases, and no obvious cause was found at operation in the remaining 22 cases.

Ten patients died in the hospital following operation; thus the operative mortality for the whole group was 34 per cent. If the two cases with hemorrhage into the brain tumor are excluded, the mortality rate drops to 30 per cent.

In 17 patients, recovery from operation permitted discharge from the hospital. Of these, five patients are working, four regularly and one part-time. Four patients show slight or little improvement in their paralysis and are invalids. Five patients are ambulatory and come to the office for recheck examination. In all, the involved hand is useless and the involved extremity is partially supported by a brace. Two patients died following discharge, one from a coronary artery thrombosis seven months later, and the second from another cerebral hemorrhage four months following discharge. One patient could not be located.

* One case was operated upon by my associate, Dr. Frederick Murtagh, Jr.

Two patients are in the hospital, one with no improvement two months following operation, the other with marked improvement two weeks following operation.

Conclusions

Spontaneous intracerebral hemorrhage usually produces symptoms and signs of a progressive expanding lesion and, in the majority of cases, is associated with bloody spinal fluid under increased pressure.

It must be differentiated from thrombosis or embolism, because treatment with stellate blocks or anticoagulants (as some advocate in cases of thrombosis) might prove fatal if used in the treatment of cerebral hemorrhage.

Although an occasional case of intracerebral hemorrhage recovers spontaneously, the majority terminate fatally. Prompt diagnosis and operation in cases showing progression in signs and intracranial pressure will save lives.

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PARENTERAL B_{12}–FOLIC ACID THERAPY IN PERNICIOUS ANEMIA *

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Introduction

The simultaneous discovery of vitamin B_{12} by Rickes and his co-workers [1] and by Smith [2] was soon followed by numerous clinical reports [3, 4, 5, 6] of its efficacy in treating pernicious anemia in relapse. Many reports, particularly those of Ungley [8] and Meacham et al.,[9] suggested that it was equally effective as a maintenance therapy. Our group,[7] however, has reported that in certain instances vitamin B_{12} alone is not a complete maintenance therapy, and the data suggested that some additional factor was necessary. Meyer [10] has reported on the effectiveness of a combination of folic acid and vitamin B_{12} orally. Bethell [11] and others have reported on the effectiveness of folic acid in certain macrocytic anemias refractory to vitamin B_{12}. Beard and McIlvaine [12] have reported that certain patients maintained over a long period of time on vitamin B_{12} showed a decline in their hemograms. The possibility that folic acid was the additional factor needed in their patients was raised. Bethell's work had suggested that both folic acid and vitamin B_{12} were necessary for a full hematopoietic response in pernicious anemia. Oral supplementation with folic acid was without effect as has been previously reported. It is the purpose of the present paper to present the results of parenteral folic acid supplementation in a group of eight patients who had been incompletely maintained on vitamin B_{12} therapy alone.

Method of Study

Eight patients known to have pernicious anemia were chosen for this study. They had all shown the usually accepted standards for pernicious anemia, that is: (1) histamine refractory achlorhydria, (2) macrocytic anemia and (3) megaloblastic bone marrow. All of these patients had shown some decline in hemograms and an increase in macrocytosis after prolonged maintenance on vitamin B_{12} alone. All but one (case 1) had had inadequate diets in at least two of the "essential" foods. All were given 1 c.c. of vitamin B_{12}-folic acid preparation † intramuscularly weekly. This preparation contained 15 micrograms of vitamin B_{12} and 1.67 mg. of folic acid. All were ambulatory patients. All were followed with weekly blood counts

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† Rubrafolin, furnished by E. R. Squibb & Sons, New York.

for the six to eight weeks that they were on therapy. The blood count included red count, hemoglobin determinations, reticulocyte counts and packed cell volumes.

Case Reports

Case 1. This 54 year old colored female was first diagnosed as having pernicious anemia in 1940. She was treated with Reticulogen until September, 1949. At that time the Reticulogen was discontinued and she was placed on 30 micrograms of vitamin B_{12}. At that time her blood count was 4,310,000, with a hemoglobin of 13 gm. and a MCV of 97.7 cubic micra. For the next nine months her red count varied between 4.6 million and 3.87 million. By June 28, 1950, after having been on 30 micrograms of vitamin B_{12} for nine months, her red count was 3,980,000, with 12 gm. of hemoglobin and a MCV of 85.5 cubic micra. She was started on vitamin B_{12}-folic acid therapy on July 27, 1950, and continued on this through October 4, 1950. At the end of this time her red count was 3.32 million, with 11.2 gm. of hemoglobin and a MCV of 120 cubic micra. Her response is shown in table 1.

Table I

		At Beginning of Rubrafolin Therapy	At End of 4 Wks.	At End of 6 Wks.	At End of 8 Wks.	At End of 10 Wks.	2 Wks. after Therapy Stopped
B. G. *Case 1*	RBC	3.6	3.91	3.35	3.30	3.32	3.35
	Hgb	11.6	11.2	10.6	10.9	11.2	11.2
	MCV	110.1	98.4	112.5	114.0	120.0	117.9
E. G. *Case 2*	RBC	3.98	3.55	3.6	3.6	3.55	3.7
	Hgb	10.2	11.3	10.4	10.7	10.5	10.8
	MCV	98.0	107.0	106.9	105.4	94.4	105.3
E. M. *Case 3*	RBC	3.9	3.8	3.9	3.8	3.6	3.45
	Hgb	12.3	21.0	12.6	12.6	12.6	10.3
	MCV	102.5	102.6	100.0	105.2	115.2	110.0
J. K. *Case 4*	RBC	3.45	3.85	3.5	3.3	3.4	3.5
	Hgb	12.4	12.4	12.8	12.0	12.0	11.2
	MCV	114.5	109.1	114.2	121.1	114.6	114.2
A. B. *Case 5*	RBC	3.5	3.3	3.2	3.7	3.55	3.65
	Hgb	11.1	12.8	11.9	12.7	11.9	12.0
	MCV	115.6	121.2	126.4	108.0	114.0	109.5
L. M. *Case 6*	RBC	3.5	3.6	—	3.0	—	3.5
	Hgb	10.6	11.0	—	11.1	—	11.2
	MCV	111.3	108.3	—	—	—	111.2
Z. T. *Case 7*	RBC	4.2	4.55	4.5	Discontinued		4.28
	Hgb	11.6	12.4	12.0	after 6 weeks		12.6
	MCV	97.7	94.5	95.6			98.4
Q. T. *Case 8*	RBC	4.4	3.8	3.9	Discontinued		3.98
	Hgb	11.5	11.0	11.7	after 6 weeks		11.3
	MCV	95.5	105.1	103.8			100.5

RBC in millions
Hgb. in gm. per cent
MCV in cubic micra

Case 2. This 72 year old colored female was first diagnosed as having pernicious anemia in July, 1941. She was placed on 3 c.c. of liver extract and discharged to the clinic. In January, 1949, she was placed on 2 c.c. of refined liver extract per week until June 24, 1949. On July 12, 1949, the refined liver was discontinued, and she was placed on 30 micrograms of vitamin B_{12}. At that time her red count was 3,960,000, with 12.3 gm. of hemoglobin and an MCV of 98.4 cubic micra; her MCHC was 31.5 per cent. From the time she was placed on vitamin B_{12} until July 14, 1950, her red count had varied from 3.2 million to 4.7 million. She was placed on one ampule of vitamin B_{12}-folic acid preparation weekly on July 27, 1950, at which time her red count was 3,980,000, hemoglobin 10.2 gm. and MCV 98 cubic micra. She remained on this therapy through October 3, 1950. During this period of time her red count was essentially unchanged, varying from 3.5 to 3.8 million. Her hemoglobin varied from 10.2 to 11.3 gm. At the end of the test period, her MCV was 94.4 cubic micra. Her response is shown in table 1.

Case 3. This 77 year old white female was first diagnosed as having pernicious anemia in September, 1940. She was placed on liver extract therapy and received 1 c.c. per week until January, 1949. At that time her liver dosage was increased to 2 c.c. weekly. This was discontinued in July, 1949, and she was started on 30 micrograms of vitamin B_{12}. At that time her red count was 3,180,000, with 11.5 gm. of hemoglobin and an MCV of 119.5 cubic micra. Vitamin B_{12} was discontinued on July 27, 1950, and she was placed on one ampule of vitamin B_{12}-folic acid mixture weekly. At the beginning of this therapy her red count was 3,900,000, with 12.3 gm. of hemoglobin and with an MCV of 102.5 cubic micra. She remained on Rubrafolin until October 6, 1950. At the termination of the test period her red count was 3.6 million, hemoglobin 12.6 gm., and MCV, 115.2 cubic micra. Her response is shown in table 1.

Case 4. This 74 year old white female was first diagnosed as having pernicious anemia in February, 1948. She was treated with refined liver and folic acid. In June, 1949, the folic acid was stopped. On August 12, 1949, she was started on 30 micrograms of vitamin B_{12}. At that time her red count was 3,120,000, with 11.4 gm. of hemoglobin and an MCV of 118.5 cubic micra. She continued to receive vitamin B_{12} until July, 1950, when she was started on vitamin B_{12}-folic acid intramuscularly. Her red count at that time was 3.45 million, hemoglobin 12.4 gm. and MCV 114.5 cubic micra. She was given Rubrafolin weekly until October 6, 1950. At the end of that time her red count was 3,400,000, with 12 gm. of hemoglobin, and her MCV was 114.6 cubic micra. Her response is shown in table 1.

Case 5. This 66 year old colored female was first diagnosed as having pernicious anemia in October, 1949. She was placed at that time on 2 c.c. of refined liver weekly. This was discontinued on July 13, 1949, when she was placed on 30 micrograms of vitamin B_{12}. At that time her red count was 3,750,000, with 12.7 gm. of hemoglobin and an MCV of 112 cubic micra. She continued on 30 micrograms until July 28, 1950, when she was started on vitamin B_{12}-folic acid. At that time her red count was 3.5 million, with a hemoglobin of 11.1 gm. and an MCV of 115.6 cubic micra. She was continued on this regimen until October 6, 1950, at which time her red count was 3,550,000, with 11.9 gm. of hemoglobin and an MCV of 111 cubic micra. Her response is shown in table 1.

Case 6. This 60 year old white female was first diagnosed as having pernicious anemia in July, 1940. She had received 4 c.c. of liver extract every two to four weeks until July 14, 1949, and her clinical course had been reported as "satisfactory." In July, 1949, she was placed on 30 micrograms of vitamin B_{12} weekly. At the start of this therapy her red count was 3.63 million, with 12.2 gm. of hemoglobin and an MCV of 111 cubic micra. She was maintained on this therapy, with occasional

supplements, until August 1, 1950, when she was placed on vitamin B_{12}-folic acid therapy. At that time her red count was 3.5 million, with 10.6 gm. of hemoglobin and an MCV of 111 cubic micra. She was maintained on this drug through September 27, 1950. At the end of that time her red count was 3 million, hemoglobin was 11.1 gm., and her MCV was 114 cubic micra. Her response is shown in table 1.

Case 7. This 51 year old white female was first diagnosed as having pernicious anemia with moderately advanced posterolateral sclerosis in July, 1948. She was given vitamin B_{12} from July, 1948, until November, 1949, at which time it was stopped for reasons unknown. On January 20, 1950, she was started on 30 micrograms of vitamin B_{12}. At the time her red count was 4,100,000, with 14.6 gm. of hemoglobin and an MCV of 102.4 cubic micra. This was discontinued and she was placed on vitamin B_{12}-folic acid therapy on August 26, 1950, at which time her red count was 4,200,000, with 10.8 gm. of hemoglobin and 97.7 cubic micra MCV. She was continued on this preparation through October 6, 1950, at which time her red count was 4.5 million, with 12 gm. of hemoglobin and an MCV of 95.6 cubic micra. Her response is shown in table 1.

Case 8. This 54 year old colored female was first diagnosed as having pernicious anemia in August, 1941. She was maintained on 2 c.c. of refined liver every two weeks and her course was described as "uneventful." She was placed on 15 micrograms of vitamin B_{12} on February 17, 1950, at which time her red count was 4.85 million, with 14.1 gm. of hemoglobin and an MCV of 90.7 cubic micra. She remained on this until she was started on vitamin B_{12}-folic acid therapy on August 25, 1950. At that time her red count was 4.4 million, with 11.5 gm. of hemoglobin and an MCV of 95.9 cubic micra. She remained on this treatment until October 6, 1950. At the conclusion of her course of therapy her red count was 3.9 million, with 11.7 gm. of hemoglobin and an MCV of 103.8 cubic micra. Her response is shown in table 1.

Discussion

Vilter et al.[13] have suggested that in the synthesis of nucleic acid from amino acids and carbon, both folic acid and vitamin B_{12} enter into the reaction at different levels and both are necessary for this synthesis. Nichol and his co-workers[14] have also pointed out the close interrelationship of vitamin B_{12} and folic acid in experimental studies. Meyer and his co-workers[10] have suggested the relationship of these two substances in pernicious anemia in relapse, but to date no one has demonstrated a clear, pure folic acid deficiency except in the macrocytic anemia of pregnancy.

The results shown by these eight patients revealed that seven of them had lower red counts and either the same or greater MCV's after they had been on vitamin B_{12}-folic acid therapy anywhere from six to 10 weeks. The one patient who did not show a drop in her red count had an increase of only 300,000 cells and a decrease in her MCV of 2.1 cubic micra. It is felt that this "improvement" is not statistically significant. Several of these patients had their dosage of vitamin B_{12}-folic acid increased to 2 c.c. per week after it was evident that they were showing no improvement on 1 c.c. Even on this increased dosage, they continued to show a decline in their red count and at least no improvement in the macrocytosis. These results with parenteral vitamin B_{12} and folic acid tend to parallel the results with oral

vitamin B_{12} and folic acid. As was pointed out by one of us (M.F.B.) in a previous paper, all of these patients except one had a diet deficient in at least two essential foodstuffs. This would tend to bear out our observation that even a combination of vitamin B_{12} and folic acid is not beneficial in controlling pernicious anemia in the face of general dietary deficiencies.

These results also suggest that in pernicious anemia in remission, even in those cases maintained on pure vitamin B_{12} over long periods, there is no demonstrable folic acid deficiency, and that, insofar as folic acid is concerned, even inadequate diets permit absorption of sufficient folic acid for the bone marrow needs.

Summary

1. Eight patients with pernicious anemia who had reached a plateau in their hemograms on parenteral vitamin B_{12} therapy were transferred to a parenteral vitamin B_{12}-folic acid preparation.

2. None of these patients showed any improvement, seven of the eight showing declines which are probably not statistically significant.

3. In this group of patients, the addition of parenteral folic acid in this dosage to their therapy resulted in no significant change in their hematologic status.

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CASE REPORTS

BACTEROIDES INFECTIONS: REPORT OF TWO CASES UNSUCCESSFULLY TREATED WITH ANTIBIOTICS *

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INFECTIONS with organisms of the genus Bacteroides have long been known in veterinary medicine and have been sporadically reported through the past five decades. Their importance as infectious agents in man has been recognized increasingly as more adequate methods of anaerobic investigation have been utilized, although the experience of any group of physicians has generally been limited to a few cases.

These organisms are commonly found on the mucous membranes of the body from whence they may invade the tissues, blood or body cavities. Metastatic abscesses often are formed when septicemia occurs. Necrosis of tissue at the primary focal lesion, with production of foul odor and tendency to spread instead of localizing, is a characteristic of bacteroides infections.

In 1945, Smith and Ropes [3] reviewed 20 cases involving bacteroides infections seen at the Massachusetts General Hospital. Etiologically they subdivided the bacteroides septicemias into two groups, the *Bacteroides funduliformis* and *Bacteroides fragilis*. The *Bacteroides funduliformis* septicemias were characterized by high mortality and metastatic abscess formation, while the *Bacteroides fragilis* septicemias ran a less fulminating course and a lower incidence of metastatic abscesses.

Beigelman and Rantz,[1] quoting Dienes, discount this difference in pathogenicity and do not differentiate the two species. These investigators point out that a considerable degree of resistance to penicillin and streptomycin may be an important characteristic of the bacteroides.

Before the advent of the more recent antibiotics, the prognosis in bacteroides infections was extremely poor. Brown, Williams and Herrell [2] reported 15 cases of *Bacteroides funduliformis* septicemias, with only one recovery. Recently, however, McVay, Guthrie and Sprunt [4] reported two such cases, with recovery following aureomycin therapy.

TECHNIC FOR CULTURE AND IDENTIFICATION OF BACTEROIDES

The ordinary technic for culturing blood specimens as employed in our laboratory was found suitable for the initial cultivation of bacteroides. A freshly heated, then cooled, 100 ml. bottle of brain-heart infusion broth containing 0.1 per cent agar was inoculated with 10 ml. of the patient's blood at the bedside. A

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Brewer's anaerobic jar was utilized for the cultivation of the bacteroides in the secondary identifying media. A cooked meat medium was found excellent for initial culture of material other than blood. The marked pleomorphism of the *Bacteroides funduliformis* was found to be in contrast with the relatively uniform appearance of the *Bacteroides fragilis* organisms.

Case Reports

Our experience in the treatment of two cases of bacteroides infections has been disappointing. Despite vigorous medical and surgical measures the patients died. Details of the cases are as follows.

Case 1. A 71 year old white woman was admitted to this hospital May 3, 1950, following two weeks of generalized malaise with myalgia and arthralgia of the extremities. She denied fever, cough or an upper respiratory infection, but her referring physician states that she had run a high fever which responded to penicillin. Examination on admission was negative with the exception that the cervix was highly inflamed. Temperature was 100.2° F., blood pressure 100/70 mm. of Hg, and pulse 86. Roentgenology of the chest was noncontributory.

During her first hospital stay the patient ran two distinct febrile courses, the initial course terminating on her nineteenth hospital day. In this first period she remained lethargic and showed a febrile reaction of 102 to 103° F. each day. Blood counts taken during this time revealed a leukocytosis ranging from 13,300 to 15,700 cells per cubic millimeter, which were approximately 90 per cent polymorphonuclear neutrophils, and a hemoglobin value which decreased from 11.5 gm. on May 4 to 10.5 gm. on May 22.

A blood culture taken May 7 grew *Escherichia coli*, while one taken May 9 yielded *Bacteroides funduliformis*. Another culture taken May 18 was positive for both organisms. Laboratory studies showed the *E. coli* was sensitive to a level of 0.975 mcg./ml. of aureomycin, while the *Bacteroides funduliformis* was inhibited by a level of 3.9 mcg./ml. of aureomycin. At this time aureomycin therapy was instituted with an initial dosage of 500 mg. every two hours for two doses, with continued dosages of 250 mg. every four hours. Until the antibiotic was started the patient was drowsy, lethargic and poorly oriented. She had moderate nuchal rigidity and a positive Kernig's sign. A purulent vaginal discharge persisted from which *E. coli*, *Aerobacter aerogenes* and *Micrococcus pyogenes* var. *aureus* were cultured.

Three days after the institution of aureomycin therapy the patient improved noticeably, becoming afebrile and alert for the first time since admission. On May 24 her sclerae became jaundiced, and an icterus index of 18 units with an indirect van den Bergh of 3.1 mg. was reported. Aureomycin was discontinued at this date.

The patient continued to improve clinically until June 8, when her temperature rose again to mark the advent of her second febrile course. Her condition once more deteriorated, and she became apathetic and uncoöperative. The temperature had a spiking course which reached a high of 104.5° F. on June 14. A blood culture taken June 13 again grew *Bacteroides funduliformis*. Aureomycin had been started again on June 12, two days previous to her peak temperature, and on June 18 the temperature came down to normal. For the duration of hospital stay the temperature remained normal or slightly subnormal. Recovery was slow following this second febrile period, the patient remaining negativistic and somewhat disoriented. She remained slightly icteric but no metastatic abscesses were detected. Aureomycin was continued during this three week period. Her hemoglobin was reported as 8.5 gm. on

July 15 and she was given whole blood transfusions. She was discharged from the hospital eight weeks after admission.

The patient was re-admitted August 15, 1950, in a greatly disoriented state. The temperature was 103° F., and she appeared to have a recurrence of her former infection. However, repeated blood cultures remained sterile. An enlarged liver suggested a hepatic abscess. Liver function tests, however, were normal. Treatment was symptomatic and in four days her temperature returned to normal and her state of orientation improved. She was observed for 19 days and was discharged in good health on September 3.

On November 17, 1950, the patient was admitted for the third time with a diagnosis of bronchopneumonia. She was extremely ill and her course was one of progressive deterioration. She died December 7. During this hospital stay icterus was again noted. A blood culture taken on this admission was negative.

Comment: The recovery of one or more species of bacteria in addition to the bacteroides in blood culture is not uncommon. In addition to *E. coli*, the streptococci, clostridia, enterococci and paracolons have been reported. Although definite proof of the location of the primary focus of this infection is lacking, we feel it probably arose in the inflamed cervix. In vitro studies of this organism proved it to be somewhat resistant to aureomycin. Clinically, however, the infection was controlled at first by this antibiotic, but the organism was only suppressed. In time it became more resistant to aureomycin and was the probable cause of death of the patient.

Case 2. A 40 year old white laborer was admitted July 4, 1950, with a chief complaint of low back pain. Past history revealed that the patient had had draining ears since early childhood, the right ear draining more than the left. About 18 months before admission he had had a sore throat and tonsillitis, for which penicillin had been administered. Following this his ears became much drier. On April 14, 1950, he experienced a recurrence of his otitis media and was again given penicillin. Two weeks later all his teeth were extracted. In May he developed a right peripheral facial palsy which cleared up within 10 days and was thought to be a Bell's palsy.

Four days before the patient was admitted to the hospital he had lifted a small boy from the floor. Almost immediately he felt a sudden, severe, acute lower back pain which radiated into both legs. The severity of the pain caused him to fall to the floor, but there was no loss of consciousness. Since then he had remained in bed, having a great deal of lower back pain with radiation into the calves. Twice he had difficulty in voiding, particularly in starting the urinary stream.

Physical examination on admission revealed that the right ear canal was filled with pus and that the drum was perforated on the left. Neurologic examination showed moderate nuchal rigidity, although it was thought this might be voluntary. The lower back muscles were in spasm, with considerable tenderness over the L4 and L5 spinous processes. Straight leg raising test was positive on both sides, by lifting the legs just a few degrees off the bed. Knee jerks and ankle jerks were present. There were no pathologic reflexes, and no definite sensory loss could be made out. The impression was that the patient had ruptured an intervertebral disc.

A few hours after admission his temperature rose to 102° F. This febrile reaction seemed inconsistent with a ruptured disc. A blood culture, taken July 5, grew an anaerobic gram-negative bacillus, later identified as *Bacteroides fragilis*. Hematologic studies showed an erythrocyte count of 3,380,000/cubic millimeter, with 10 gm. of hemoglobin and a leukocytosis of 17,500 per cubic millimeter, with 91 per cent polymorphonuclear neutrophils. Meningitis was suspected and a lumbar puncture was performed. The spinal fluid was milky in color and contained a white,

rather thick coagulant material which made it difficult to obtain an accurate cell count. *Bacteroides fragilis* was cultured from this material.

The patient's temperature subsided following large doses of penicillin, and the impression was that he had a meningitis secondary to a mastoiditis. On the fourth hospital day a radical mastoidectomy was performed. Culture of material taken at operation again revealed *Bacteroides fragilis*. Postoperative fever subsided under chemotherapy, and for the remainder of this hospital stay he was afebrile. The mastoid healed promptly and the patient was discharged July 29.

On August 14 he was re-admitted to the hospital. He had had two elevations of temperature while at home but had been able to get about until the day of admission, when he had a sudden rise of temperature and a recurrence of the low back pain with radiation into his legs. He had been unable to void during the day and his legs were rapidly becoming paralyzed.

On examination, the neck was very stiff and there was a small amount of drainage in the right ear. His temperature was 98° F. on admission but within a few hours had risen to 103° F.

Neurologic examination showed almost complete paralysis of the legs, with knee jerks absent. The bladder was distended to the umbilicus. There was now a bilaterally positive straight leg raising test and a positive Kernig's test. The mental state was cloudy, the patient being very irritable and disoriented. On lumbar puncture, thick pus was obtained by aspiration. On culture this grew an anaerobic streptococcus and *Bacteroides fragilis*. Blood studies showed a leukocytosis of 13,200 cells per cubic millimeter, with 90 per cent polymorphonuclear neutrophils.

A lumbar laminectomy was performed at once and an extensive intradural abscess was found involving the cauda equina, the roots of which were bound down in a mass of greenish, foul smelling pus. This was loculated in small pockets of 2 to 10 ml. each. Following this procedure, convalescence was protracted and marked by bouts of high fever. Penicillin was found to be relatively ineffective, so streptomycin was substituted. Aureomycin and chloromycetin were also given, with chloromycetin thought to give the best results. During the next month improvement was gradual, and on September 23 he was discharged to continue convalescence at home. When seen as an outpatient, his lumbar wound had healed completely, bowel movements were normal, urinary incontinence had disappeared and his strength was good.

On November 12 the patient returned to the clinic complaining of severe vertigo and unsteadiness which had been present for several days, together with blurring of vision and numbness of the right side of the face. There had been no drainage from the ears. On this occasion he was wide awake and alert. Nystagmus on lateral gaze with the slow component to the right was noted. There was definite hypesthesia on the entire side of the face, with loss of the corneal reflex. It was a little difficult to tell why he was having diplopia, although it was thought he probably had a weakness of the right sixth nerve. There was a definite lid lag on the right side which may have been old but seemed more marked than on previous admissions. There was marked unsteadiness on Romberg, with falling to the left. Ataxia of the right arm was marked.

The patient was once more admitted to the hospital. Temperature was 97° F. at the time of admission. Chloromycetin was started and he was observed for four days. Roentgenography of the skull showed definite erosion of the right petrous apex. It was thought that he had petrositis with Gradenigo's syndrome. At this time a blood count showed only 6,500 leukocytes per cubic millimeter, with 66 per cent being polymorphonuclear neutrophils. On the fourth day after admission the mastoid incision was reopened and an attempt was made to drain the petrous process through the temporal bone. This was not successful. Some bone was rongeured

away over the posterior part of the temporal lobe and an attempt was made to reach the petrous apex extradurally underneath the temporal lobe. The dura was elevated as far as the root of the fifth nerve without encountering pus. A pack was left in the wound and the wound was closed. The postoperative course was benign, the wound healing quickly. The patient was discharged December 9 but was still unsteady and had considerable numbness of the face. He was followed at weekly intervals in the nose and throat clinic and his ear appeared to be healing without complication.

On December 30 he was again admitted to the hospital. He had seemed well until two days before, when he became stuporous and began vomiting. This occurred shortly after his ear had been irrigated. He then complained of pain in the neck and snoulders, and on the morning of admission had become very drowsy. The temperature on admission was 103° F.; the patient was very ill and disoriented and had a stiff neck. Facial weakness was more marked than formerly. The hypesthesia was still present. Nystagmus with a slow phase to the right was still present, and bilateral papilledema was found on ophthalmoscopic examination. There was no definite weakness of the arms but the right leg was almost flaccid. There was clonus at the left ankle and a Babinski's response in the left foot. As nearly as could be determined, the visual fields were full. Roentgenography of the skull showed a pineal in the midline, without shift. Our impression was that the patient had a cerebellar abscess.

He was started once more on chloromycetin and was given fluids. His condition improved, although he ran a spiking temperature which reached 103° F. on several occasions. He continued to be very drowsy, but the vomiting stopped and with intravenous fluids he became better hydrated. On the sixth day of hospitalization he was taken to the operating room, where an occipital burr hole was placed and an abscess was struck deep in the right cerebellum, probably near the cerebellopontine angle; about 6 or 7 ml. of foul smelling pus were obtained. It was similar to that obtained from the spinal canal on previous operation. A little Thorotrast was installed into the cavity and the wound was closed.

Antibiotic sensitivities were done on the *Bacteroides fragilis* which was cultured from this pus. The organism was inhibited by a concentration of 0.47 mcg./ml. of chloromycetin, and by concentrations of less than 0.11 mcg./ml. of aureomycin and terramycin. Streptomycin was found to inhibit growth only when a level of 250 mcg./ml. was attained. Postoperatively, the patient was tried on terramycin but continued to run a spiking fever of 102 to 103° F.; later, aureomycin was added, with good results. However, the papilledema persisted and the patient's legs became weaker. On January 29, 1951, through a cerebellar approach, a marked arachnoiditis around the right cerebellar pontine angle was found. There was no evidence of a cerebellar, pontine or arachnoid abscess. The incision was closed and the patient's postoperative course was extremely benign. He continued to run a low grade fever until all medications were stopped, when the temperature promptly subsided and remained normal during the rest of his hospital stay.

At the time of discharge he was clearing mentally, and had no vomiting, no headache and no bulging of the cerebellar decompression. The legs, however, were still almost completely paralyzed. Bowel movements and urination were controlled but the papilledema remained high. We thought the latter might be due to an optic neuritis.

The patient was not seen again at the clinic but a letter from his wife furnished the following information. The first week after discharge from the hospital he gained weight and showed some improvement. However, for the next eight weeks his course was downward and marked by periods of mental confusion. He died April 18, 1951, following a period of coma. Nuchal rigidity was observed at this time but the temperature did not rise over 100° F. Unfortunately, a postmortem was not obtained.

Comment: This case represents an unusual etiologic agent causing brain and intradural spinal abscesses. From in vitro studies, the cultured organism should have been amenable to treatment with antibiotics. Nevertheless, it is apparent that surgical drainage of abscesses remains of primary importance, with the use of selected antibiotics as an important adjunct of therapy. Despite these measures, the infection was suppressed only for short periods, persistently recurring and finally causing death.

Discussion

Bacteroides is one of the many saprophytic organisms that become pathogenic only under unusual circumstances. As previously mentioned, it is usually found in conjunction with other organisms. One would suspect that it becomes dominant only after a lesion has been produced by a more virulent organism.

Like many saprophytic organisms, it displays great resistance to therapeutic agents. In both instances in the cases described above, the progress of the infection could be temporarily halted but could not be eradicated. A tolerance to the antibiotics was soon gained, and the body resources appeared to lack an efficient mechanism in combating the microörganism.

How the bacteroides became established in the first case is not at all clear, but it appears likely that the inflamed cervix may have been the point of entry. In the second patient, the chronically infected ear seems to be the site from which the infection spread. One may postulate that the organism was released from control when the initial penicillin was given, which killed off the more pathogenic organisms and allowed the less virulent saprophytes to become dominant. In both cases, once the bacteroides had become firmly established, large amounts of antibiotics and, in the second case, surgery, were of no permanent avail.

In conclusion, we wish to present our experience with a limited number of cases. Despite the favorable reports in the literature, it would appear that bacteroides infections frequently do not respond to treatment by antibiotics, despite their seeming sensitivity in in vitro tests.

Also, a word of caution is extended when penicillin or some other antibiotic is indiscriminately given for some acute benign process. Should the patient have, in addition, an old chronic infection, such as a draining ear, osteomyelitis or infected fistula, the pathogen may be killed but, in exchange, a benign saprophyte may proliferate and set up an uncontrollable infection.

Summary

Two cases of bacteroides septicemia are presented. The effect of various antibiotics on the clinical course of these patients and in vitro studies of the efficacy of these agents in the inhibition of the causative organisms are described. Despite vigorous antibiotic therapy and surgery, both patients succumbed to the infection.

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BRUCELLA ARTHRITIS OF THE HIP JOINT: A REVIEW OF THE LITERATURE AND REPORT OF A CASE TREATED WITH TERRAMYCIN *

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Brucellosis in man has become a serious problem in the agricultural areas of the United States and Canada. Accordingly, much has been written about the epidemiology, pathology, general manifestations, diagnosis and control. Less attention has been paid to the localized effects. Although fleeting arthralgia is a common feature of acute brucellosis, destructive bone and joint lesions are less familiar, partly because of their rarity and partly because of the difficulty in establishing the diagnosis.

Several types of bone and joint lesions have been described in undulant fever. The commonest form of joint involvement is a generalized polyarthritis. In a study of brucellosis in Iowa, Hardy [1] noted that arthralgia appeared in 32 per cent of 375 patients. In these cases multiple joints were involved, with the pain shifting from one joint to another, usually with no demonstrable objective changes. In addition, about 2 per cent showed evidence of actual inflammation, with red, painful and swollen joints. Complete subsidence of these arthritic manifestations was the rule.

Intermittent hydrarthrosis as a complication of the disease has been described by Baker,[2] Sharpe [3] and Hardy.[4] In the case described by Baker, the patient developed massive, relatively painless swelling of the knees at seven day intervals over a period of several months. *Brucella abortus* was cultured from synovial fluid withdrawn from the affected joints.

It has been established, both by experiment in animals and by clinical observations on human cases, that brucella infection may cause an eroding suppurative arthritis,[4, 5] most frequently involving the spine. Steindler [5] surveyed the literature in 1940 and found 57 cases of osteomyelitis involving the spinal column and intervertebral discs. To these he added four more cases. Osteomyelitis of the long bones has also been recognized.[6]

It should be emphasized that although arthralgia is common, and acute septic joint lesions have been demonstrated in acute brucellosis, not a single case of

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chronic arthritis resulting from a brucella infection has been encountered in the experience of Spink in Minnesota.[7]

The frequency and nature of arthritis in undulant fever vary widely depending on the strain of organism involved. Hardy [4] found the complication of arthritis rare in guinea pigs inoculated with the abortus strain, whereas with the inoculation of the suis strain, suppurative arthritis and spondylitis were relatively common. The experience of the Hardy group in Iowa with human cases appeared to confirm these experimental observations. Arthritic complications were found to be rather rare in the milder infections caused by the abortus strain. In the more severe form of the disease associated with infection by the suis strain, joint involvement was common, but apparently less so than with the melitensis infections observed in Mediterranean and Mexican regions. Spink [7] has stated views that are diametrically opposed to those of Hardy on the basis of his experience in Minnesota, where the majority of cases were due to *Brucella abortus*. In these cases, osseous involvement was found to be a fairly frequent complication.

Destructive bone and joint lesions are considered to be an uncommon complication of brucellosis in man. Among the reported cases of brucella arthritis there are eight instances of hip joint involvement. In only two of these was the diagnosis of brucella infection confirmed by culture of the organism from the blood, synovial fluid or synovial tissue. We propose to review the literature on brucella infection of the hip and to report a case with positive blood and bone marrow cultures treated with terramycin.

Review of the Literature

The first report of involvement of the hip joint by brucellosis was contained in a thesis submitted in 1911 by Strachan to the University of Glasgow, Scotland.[8] This thesis, relating his experience with brucellosis in South Africa, reported a case of hip joint disease requiring treatment in bed with extension. A similar case, treated by Dr. A. Garrow, of Steytlerville, Cape Colony, in 1910, was also recorded in this thesis. The details of the diagnosis and recovery of these patients are not available.

In 1921, Cignozzi [9] reported two cases in children of undulant fever, complicated by hip joint disease. Both of these cases resembled a typical tuberculous process except that they recovered full function after serotherapy.

The first report of brucella infection of the hip confirmed by culture of the organism from pus obtained from the joint was published in 1933 by O'Donoghue.[10] This was a girl of 12 who developed severe hip pain while she was acutely ill with brucellosis. Brucella agglutination tests on the serum were positive in dilutions of 1 : 160. Roentgenograms showed a slight cloudiness of the right hip, with probable bulging of the joint capsule. A radical drainage was done and a large amount of pus evacuated. *Brucella melitensis* was cultured from this pus. Immobilization of the hip for several months in a plaster spica resulted in ankylosis.

From France, Ramseyer [11] published in 1946 the report of a severe destructive arthritis of the hip complicating undulant fever in a boy of 12. Severe hip pain developed during the acute stage of the illness. Roentgenograms revealed marked destruction of the head and neck of the femur and of the acetabulum. The serum agglutination titers were positive on two occasions in dilutions of

1:20 and 1:1,280. No material was obtained for culture. The child was treated with serotherapy and hip extension. A solid bony ankylosis was demonstrated 21 months after the onset.

The most complete report to date was published in 1949 by Coventry et al.[12] This patient, a 22 year old farmer, complained of hip pain for 11 weeks. On admission to hospital his temperature ranged from 99° to 102° F. Brucella agglutinations were positive in dilutions of 1:800, while blood cultures were consistently negative. Roentgenograms showed osteoporosis of the head of the femur and evidence of an early destructive arthritis. The hip joint was inspected surgically. There were marked early degenerative changes in the articular cartilage covering the head of the femur. The joint was filled with a thick, glairy, slightly cloudy fluid. The synovial tissue was thick and boggy. Cultures of the synovial fluid were negative, whereas cultures of the synovial tissue proved to be positive for *Brucella suis*. The patient was kept in a hip spica for nine weeks and received combined therapy with sulfadiazine and streptomycin. No weight bearing was allowed for nine months. Complete roentgenologic healing was demonstrated 18 months after the onset, and the patient complained of no disability.

The most recent case has been reported by Ploussard.[13] This patient developed persistent and progressive pain following a severe wrench of the hip. Three months later the patient was admitted to hospital, where he manifested a temperature of 98° to 99.6° F. Brucella agglutinations of the serum were positive in all dilutions, but no material was obtained for culture. Roentgenograms of the hip showed a localized area of bone absorption or destruction in the head of the femur. The type of treatment used is not reported, but within a year the patient was symptom free, and roentgenograms of the hip demonstrated complete healing.

Case Report

A married farm laborer, aged 57, was admitted to the Winnipeg General Hospital on June 10, 1950, complaining of extremely severe pain in the right hip which had been present for one month. He had worked on dairy farms for the greater part of his life, and made a practice of drinking raw milk. From November, 1948, to June, 1949, he had worked on a dairy farm where several cows had aborted. In October, 1949, a large part of his job was feeding pigs on another farm. At this time he began to notice marked fatigue and some loss of weight. In May, 1950, this fatigue became more severe and he noticed some pain in the right hip and knee. The pain in the hip was severe enough to cause him to limp noticeably. The pain was intermittent, worse when he was standing or walking and diminished when he lay down. It was of a deep aching quality, felt mainly over the right sacroiliac joint and in the right groin. About this time a soft, fluctuant, painless swelling appeared over the left olecranon and left patellar bursae. On June 9 the pain in the right hip became unbearable and the patient was unable to continue working. At this time his weight had dropped from 150 pounds in June, 1949, to 126 pounds on admission to hospital (June, 1950).

Past history revealed an attack of gonorrhea in 1943. He received treatment for this during the acute phase, with immediate and permanent relief. In addition, the patient had been admitted to hospital in 1947 with a very painful right shoulder. He was unable to lift his arm more than 20 degrees. Roentgenograms of the shoulder were negative. No diagnosis was made. He received no treatment and the condition gradually cleared over a period of three months.

On admission the patient appeared slightly disoriented and confused. His

temperature was 100.4° F. and he appeared chronically ill and in severe pain. His attention wandered and his thoughts appeared to be far away. He was emotionally labile, often moved to attacks of unexplainable tears and bouts of anxiety. Examination revealed localization of the pain to the right thigh and groin. The inguinal lymph nodes were palpable. The liver was palpable one inch below the costal margin, with a firm, smooth, nontender edge. The spleen was not palpable. The results of the remainder of the general examination were normal except for the right hip area. The patient lay with his right leg slightly flexed at the hip and markedly externally rotated. Active and passive movements at the right hip joint caused great pain. The olecranon and patellar bursae were enlarged, soft, reddened and nontender. Thus it

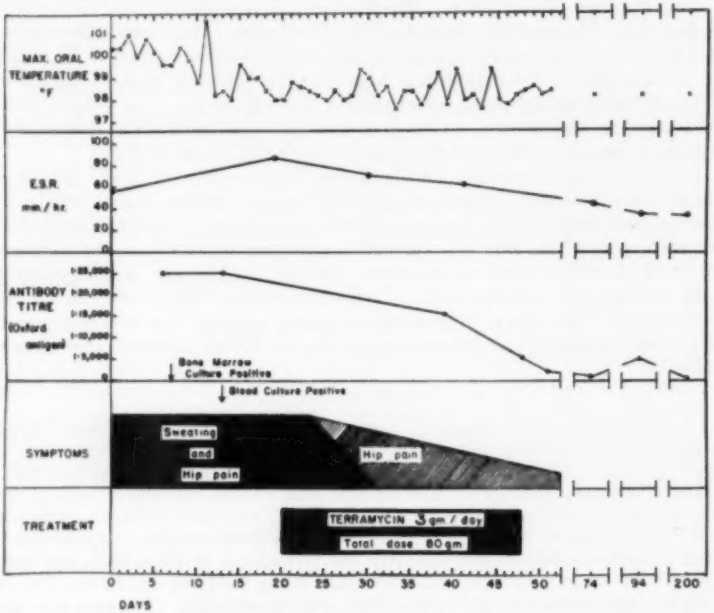

FIG. 1. Correlation of clinical manifestations and laboratory findings with treatment.

is seen that history, symptoms and physical signs were identical to those produced by tuberculosis of the hip joint.

Figure 1 summarizes the principal clinical features of his illness. The temperature is seen to range between 98° and 99° F., except for a few occasions during the first week, when it rose to 100° and 101° F. During his stay in hospital the urinalyses were all normal. The Wassermann reaction was negative. The concentration of hemoglobin on admission was 13.4 gm. per cent. On admission the leukocytes numbered 6,400 per cubic millimeter of blood. They varied between this figure and 3,500 per cubic millimeter during his stay. The sedimentation rate was 58 mm. per hour (Westergren) on admission and dropped to 44 mm. on discharge from the hospital. The Mantoux reaction was negative, with 1:10,000 and 1:100 dilutions of old tuberculin. The serum agglutinations were positive to 1:25,000, with sus-

pensions of *Brucella abortus* on the fifth day of admission. This titer remained elevated for some time and then began to fall as shown. A bone marrow culture, taken on the seventh day, was positive for *Brucella abortus*, and a blood culture taken on the thirteenth day was also positive. Thereafter, bone marrow and blood cultures, as described later, were consistently negative. Roentgenograms of the thorax and abdomen were negative. In addition, a roentgenogram taken of the pelvis on the second day of admission (figure 2) was negative except for "sacralization" of the fifth lumbar vertebra on the left side. However, on the twenty-seventh day (figure 3), a repeat film of the pelvis showed almost complete destruction of the articular margin of the right acetabulum and some narrowing of the joint space. Radiologi-

FIG. 2. June 10, 1950. Hip joints normal.

cally these changes appeared consistent with a septic arthritis. Repeated films on the forty-seventh, sixty-ninth and seventy-fourth days showed little change.

The patient's course in hospital was one of very gradual improvement. He was treated with 3 gm. of terramycin daily, starting on the twentieth day and continuing for 28 days. In addition, hip traction was applied from the thirty-second to the fifty-ninth days. When the traction was removed he still complained of a deep aching in the hip; however, this was considerably less than on admission, and he was able to walk comfortably. Seventy-four days after admission the patient was discharged from hospital (August 27, 1950).

Three weeks following discharge from hospital the patient returned. He had started to do part-time work on a farm and was feeling well. His temperature was normal, the sedimentation rate remained at 40 mm., and the agglutination titer had fallen to 1:5,000. Four months after discharge (December 26, 1950), he again

FIG. 3. July 8, 1950. Articular margin of the right acetabulum has almost disappeared.

FIG. 4. December 26, 1950. The right acetabular margin is restored.

returned. There had been a gain in weight of 29 pounds and he complained of no hip pain whatsoever. He was able to do full time farm labor with no excessive fatigue. On this visit, the sedimentation rate was still 40 mm. per hour, but the agglutination titer had fallen to 1:500. A roentgenogram of the pelvis (figure 4) showed radiologic healing of the right hip joint. Agglutination titer 10 months after discharge (June, 1951) was 1:250.

Laboratory Diagnosis

Three laboratory procedures are commonly used in the diagnosis of undulant fever: (1) isolation of the organism; (2) serum agglutinations with standard suspensions and (3) skin sensitivity test. The opsonocytophagic reaction and bactericidal test have been used less extensively.

The most conclusive diagnostic method is the isolation of the causative bacterium. The difficulty of isolation is dependent primarily on the intracytoplasmic existence of the organism in mesenchymal tissues, with infrequent showering of small numbers into the blood stream. The fastidious nature of the bacterium on primary culture and its slow growth are discouraging. The cultures may not show growth for a month, and must frequently be discarded as contaminated as a result of repeated subculturing.

In this patient, blood and bone marrow samples were obtained for culture on the seventh day of admission. Gram-negative coccobacilli were recovered from the marrow culture on the eighth day of incubation; these were later identified as *Brucella abortus*. The blood culture remained negative. Four more blood cultures were taken prior to the beginning of therapy and before the marrow culture became positive. Of these, *Brucella abortus* was recovered from one, taken on the thirteenth day of admission. Three blood cultures and one marrow culture taken after the eleventh day of treatment were negative.

The percentage of positive cultures in this laboratory has improved by repeated blood cultures in the early stage of an exacerbation and by the use of bone marrow cultures. The incidence of contamination of cultures has been decreased by the use of milk dilution bottles (Pyrex, Catalogue No. 615–180 ML) with perforated metal caps, containing a rubber diaphragm; a Bacto-tryptose agar slant is made in the bottle prior to the introduction of sterile Bacto-tryptose broth. In this way, subcultures can be made by tilting the broth on the agar every other day without removing the cap. Incubation is in an atmosphere of 10 per cent carbon dioxide.

Identification is based on dye tolerances and agglutination with homologous immune serum. In the case presented above, growth occurred on basic fuchsin (1:25,000) and not on carbol thionin (1:35,000); both of which were incorporated in Bacto-tryptose agar plates. Differentiation is usually made by agglutinin absorption technics; identification is sometimes difficult when the picture of species gradation is obtained from both serologic analysis and dye tolerances.

The serum agglutination reaction is not so conclusive as the isolation of the organism but is of great value in many cases. A titer of 1:500 or greater is practically diagnostic; a titer of 1:200 is significant when supported by good clinical evidence of the disease.

The Lederle Febrile Antigen (*Brucella abortus*) with the rapid slide technic of Huddleson and Abell [14] is a useful presumptive procedure and in this case agglutinated to the highest dilution (1:640). Critical serum titrations by the tube dilution method, using antigens obtained from the Standards Laboratory,

School of Pathology, University of Oxford, showed an initial serum titer of 1 : 25,000 (*Brucella abortus* suspension). Serum agglutinations were repeated at eight to 10 day intervals for the first two months and showed a gradual decline in antibodies, with a final titer of 1 : 250 eleven months after the onset of therapy.

The intradermal test was not used in this case for two reasons: It invalidates to some extent the agglutination reaction, which is a much more dependable diagnostic procedure, and also it was feared that the patient might be subject to a severe local and/or general reaction.

Treatment

The evaluation of therapy in brucellosis is rendered difficult because of the relapsing course of the disease, and the tendency of the organism to lie dormant for prolonged periods in certain tissues such as the spleen. What appears to be adequate chemotherapy during the acute phase often proves merely to have checked temporarily the course of the disease. The distressing symptoms of fever, sweating, fatigue and joint pains may be relieved; however, unless the dosage has been adequate and given over a prolonged period, a relapse may develop a few weeks or months later.

Experimental studies with terramycin have demonstrated a bacteriologic spectrum almost identical with that of aureomycin.[15, 16] As aureomycin has a marked bacteriostatic effect on brucella both in vitro and in vivo,[17, 18, 19] it was expected that terramycin would also be effective against these organisms. Chas. Pfizer & Co., Inc., in whose research laboratories terramycin was discovered, report[20] personal communications with Spink and Heilman to indicate that terramycin is highly effective in vitro against *Brucella abortus, Brucella suis* and *Brucella melitensis*. It was therefore considered feasible to observe the response of the above reported case to terramycin.

Terramycin, in divided doses amounting to 3 gm. daily, was started on the twentieth day. Within five days there was significant clinical improvement. The sweating and fatigue disappeared rather quickly. There was marked improvement in the mental confusion and emotional instability. The temperature varied as demonstrated in figure 1, never rising above 99.4° F. after the terramycin was started. Three blood cultures and one bone marrow culture taken after treatment was begun were negative. During the ensuing 10 months the agglutination titer fell from 1 : 25,000 to 1 : 250; the patient gained 29 pounds in weight and there was symptomatic and radiologic healing of the destructive changes in the right hip joint. To date the patient has been followed for 11 months with no evidence of a recurrence. We feel that the administration of terramycin in this case was definitely beneficial.

Discussion

Brucellosis of the hip joint, although not common, presents a rather constant clinical picture that should be recognized. Joint involvement occurs during the acute febrile phase of the disease and is always monarticular. As Cignozzi observed in 1921,[9] the local signs, symptoms and roentgenologic appearance of the hip joint resemble those of a tuberculous infection, except that with a brucella infection the joint shows a tendency to heal.

The early stage of a brucella infection of the hip joint is marked by a slight limp. Signs of irritation become more marked, and muscle spasm in all directions increases. The thigh becomes flexed, adducted and externally rotated. Roentgenologic examination reveals capsular swelling, bulging of the joint capsule and destruction of the femoral head or acetabulum, or both. The diagnosis of undulant fever, of course, depends upon the growth of brucella from blood cultures, and to confirm the etiology of the septic arthritis a culture of the organism from the joint fluid or synovial tissue should be obtained. In the present case, the diagnosis is presumptive as regards the hip joint, since the organism was not recovered from the joint itself.

The prognosis is good. Three cases described in the literature [1, 13] received no chemotherapy and still made complete recoveries. In two other cases,[10, 11] a bony ankylosis resulted following immobilization for several weeks in a plaster spica of hip extension and without chemotherapy. With adequate chemotherapy, it would appear that recovery can be obtained in all cases. In a case treated with a combination of sulfadiazine and streptomycin,[12] roentgenologic healing was demonstrated within 18 months. On the basis of the case reported in this paper, it would appear that terramycin is also effective, since roentgenologic and functional healing was demonstrated within six months.

Summary

1. The literature related to brucellosis of the hip joint has been reviewed. To date there have been eight cases reported. The diagnosis was confirmed by recovery of a brucella organism from the hip joint in two of these cases. These two cases represent infection by the melitensis and suis strains.

2. A case of septic hip joint disease complicating an acute infection by *Brucella abortus* has been presented. The diagnosis of undulant fever was confirmed by the culture of *Brucella abortus* from the blood and bone marrow. Recovery of the organism from the hip joint was not attempted.

3. Terramycin therapy was promptly effective in controlling the acute infection. Complete radiologic and functional healing was demonstrated within six months. As there has been no recurrence of symptoms during the ensuing 11 months, it is considered that terramycin has effected a probable cure in this case. Terramycin was given in dosage of 0.5 gm. approximately every four hours for 28 days, a total of 80 gm. being administered.

4. The laboratory methods of diagnosis have been summarized.

5. The clinical picture and prognosis of brucellosis of the hip joint have been discussed. In particular, it must be distinguished from tuberculosis of the hip.

Addendum

Since the above report was submitted the patient has been observed for an additional year and there has been no recurrence of symptoms. During this period an additional case has come to our attention. Eales (South African M. J. 25: 143, 1951) has reported apparent recovery from brucella arthritis of the hip in an eleven year old boy treated with aureomycin. In this patient *Brucella melitensis* was cultured from the blood.

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EFFECT OF ACTHAR-C (ACTH) IN SARCOIDOSIS *

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THE treatment of sarcoidosis has been noteworthy for the large variety of therapeutic agents employed, generally without effect. More recently, attention has been directed to the possible value of cortisone and ACTH in the therapy of

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this disease.[1] Thorn and his associates [2] administered 40 mg. of ACTH for eight days to a patient with sarcoidosis, with no effect on the pulmonary lesions. In another report,[3] marked improvement of uveitis was noted in two patients with suspected sarcoidosis treated by ACTH. In one of these patients, no change was observed in the pulmonary involvement. The first impressive effect of these drugs on sarcoidosis was reported by Sones et al.[4] They described prompt and marked improvement in pulmonary, cutaneous, lacrimal, parotid and lymph node lesions in two patients. They noted that they had obtained a better therapeutic response with cortisone than had been described for ACTH in the therapy of sarcoidosis. Shortly thereafter, Thorn and his associates [5] reported considerable clearing of pulmonary lesions in a case of sarcoidosis treated by 20 mg. ACTH given intravenously for 15 days. A subsequent report [6] described the use of ACTH given both intramuscularly and intravenously to a patient with sarcoidosis. No mention is made of the effect on the lung involvement.

In a report on the use of ACTH in a variety of disease conditions,[7] one case of sarcoidosis was treated without effect.

The reports on the value of cortisone and ACTH in sarcoidosis are therefore meager. Up to the present time, only one case [8] treated with ACTH has been reported in sufficient detail to evaluate the effect of the drug. It is the purpose of this paper to report on the intensive and prolonged use of ACTH in a patient with marked pulmonary sarcoidosis, and on the pathologic changes that occurred after the use of the drug. Although studies on other cases are being carried out, it is felt that detailed observations on one case may be helpful.

Case Report

A 48 year old Negro male was first admitted to the Jewish Memorial Hospital on February 2, 1949, complaining of morning cough and expectoration for the preceding four years. He had lost seven pounds in the previous three months. He had noted a low grade fever for several weeks. Chest roentgenograms preceding his admission had disclosed moderate hilar adenopathy. There was no history of exposure to tuberculosis, occupational dusts or silica. Physical examination on admission revealed râles over the right upper chest anteriorly and at both lung bases. The tonsils were hypertrophied. The liver and spleen were not palpable. The lacrimal and parotid glands were normal. There was no evidence of peripheral lymphadenopathy. The fingers were not clubbed.

Laboratory studies revealed a sedimentation rate of 78 mm. in one hour. The blood count was normal. Sputa and gastric examinations were negative for tubercle bacilli. Total blood proteins were 8.5 mg. per cent; serum albumin, 3.5 mg per cent; serum globulin, 5.0 mg. per cent; A/G ratio, 0.7. The Mantoux test was negative to 1 mg. old tuberculin. The chest roentgenogram revealed multiple fine irregular infiltrations scattered throughout both upper lung fields. There was a marked increase in the hilar densities, suggesting hilar adenopathy. X-rays of the hands and feet were normal.

A diagnosis of Boeck's sarcoid was made. Sternal marrow puncture revealed no pathologic findings. A tonsillectomy was done. No evidence of sarcoid infiltration was found in the resected tonsils. The temperature was slightly elevated throughout the patient's hospital stay. After 17 days, he was discharged unimproved.

After discharge, he was asymptomatic except for a mild, moderately productive morning cough. However, chest roentgenograms taken at rather frequent intervals revealed progressive diffuse involvement of the parenchyma of both lungs and marked

gradual enlargement of the mediastinal glands on both sides. In June, 1951, he developed symptoms suggestive of diminished pulmonary efficiency, became dyspneic on slight effort, and finally orthopneic during the week or two before his second admission to the hospital. At no time was there evidence of congestive heart failure. His lips and finger tips became cyanotic.

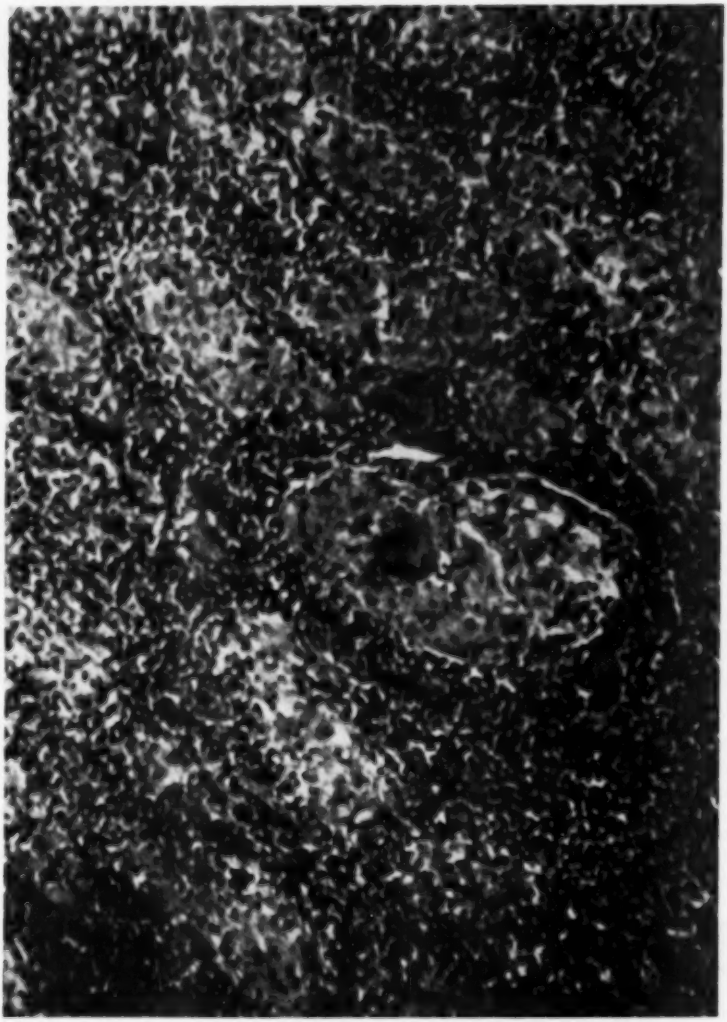

FIG. 1. Right femoral lymph node before ACTH therapy, showing sarcoid infiltration.

He was readmitted to the hospital on June 26, 1951. Physical examination revealed crepitant râles at both bases. He was moderately orthopneic, cyanotic and dyspneic. The spleen was palpable and soft, about one fingerbreadth below the left costal border. There were soft, nontender nodes in both inguinal and femoral regions. The neck veins were not distended. The liver was not palpable. His temperature was 101° F.

A biopsy of one of the femoral glands was done and showed typical features of Boeck's sarcoid (figure 1).

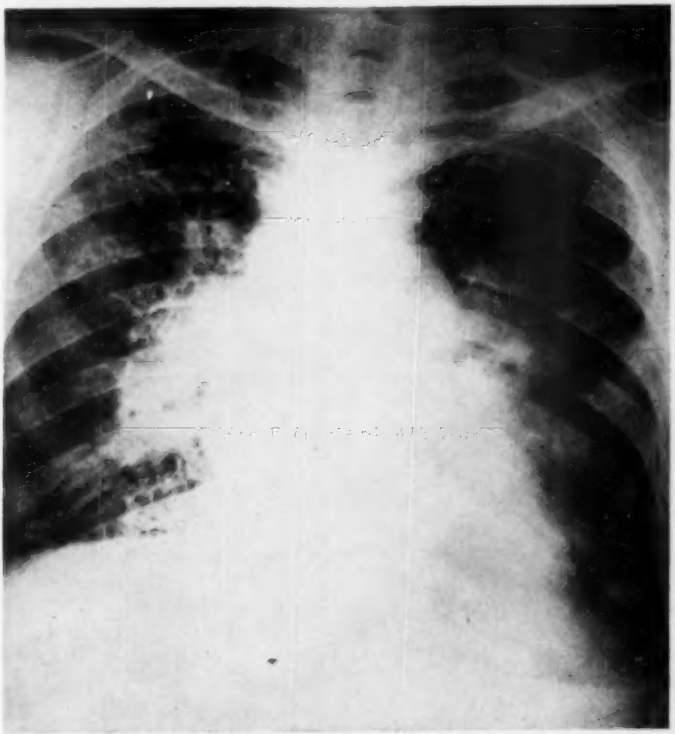

FIG. 2. Chest x-ray before ACTH therapy, showing diffuse infiltrations in both lungs and marked hilar enlargement.

A chest roentgenogram on June 26, 1951, showed diffuse infiltrations of both lungs, with marked widening of the mediastinal shadow in which one could discern large nodulations characteristic of hilar adenopathy (figure 2). After one week during which control studies were done, Acthar-c * therapy was instituted. Acthar-c

* Armour and Co. brand of adrenocorticotropic hormone derived from sheep pituitary. Acthar-c was generously donated through the cooperation of Dr. Harley Cluxton, Jr., Director of Medical Research, Armour and Co.

was given intramuscularly at six hour intervals, beginning with a dose of 20 mg. daily. The dose was increased at weekly intervals until a dose of 80 mg. daily was being given.

Subjective improvement was obvious almost immediately. The fever subsided, evidence of pulmonary insufficiency disappeared, and the patient began to gain weight. The spleen became impalpable at the end of the second week. Roentgenographic improvement occurred minimally during the first three weeks of therapy.

During the fourth week of therapy, at a time when he was receiving 80 mg. of Acthar-c daily, and coincidental with a marked fall in circulating eosinophils, the

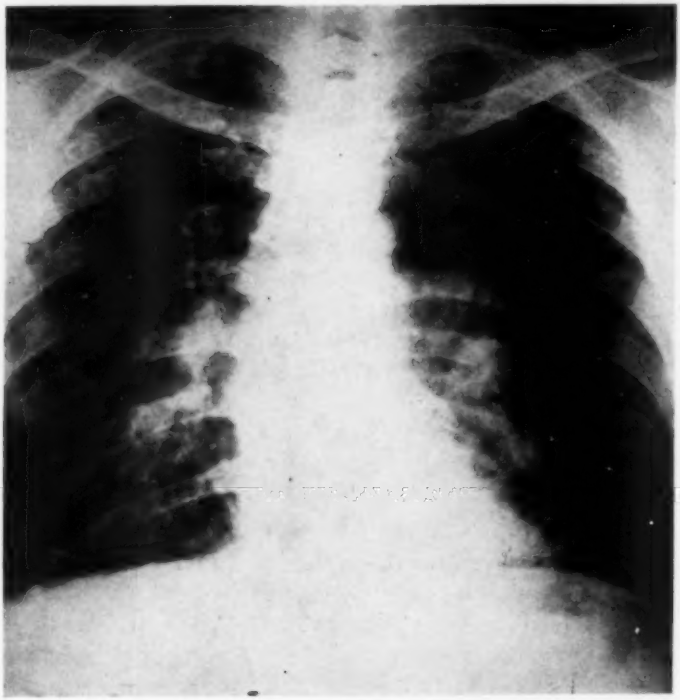

FIG. 3. Chest x-ray after ACTH therapy, showing disappearance of mediastinal enlargement and regression of pulmonary densities.

chest roentgenogram showed marked regression of the parenchymal and mediastinal shadows. The signs in the lungs disappeared except for some residual subcrepitant râles at the right base.

Because of the persistence of some parenchymal densities, and in order to evaluate comparatively the effectiveness of intravenous administration of Acthar-c, it was decided to change to this latter mode of therapy.

Intravenous Acthar-c was given according to the method described by Thorn and his associates.[8] Twenty-five milligrams of Acthar-c were given intravenously in

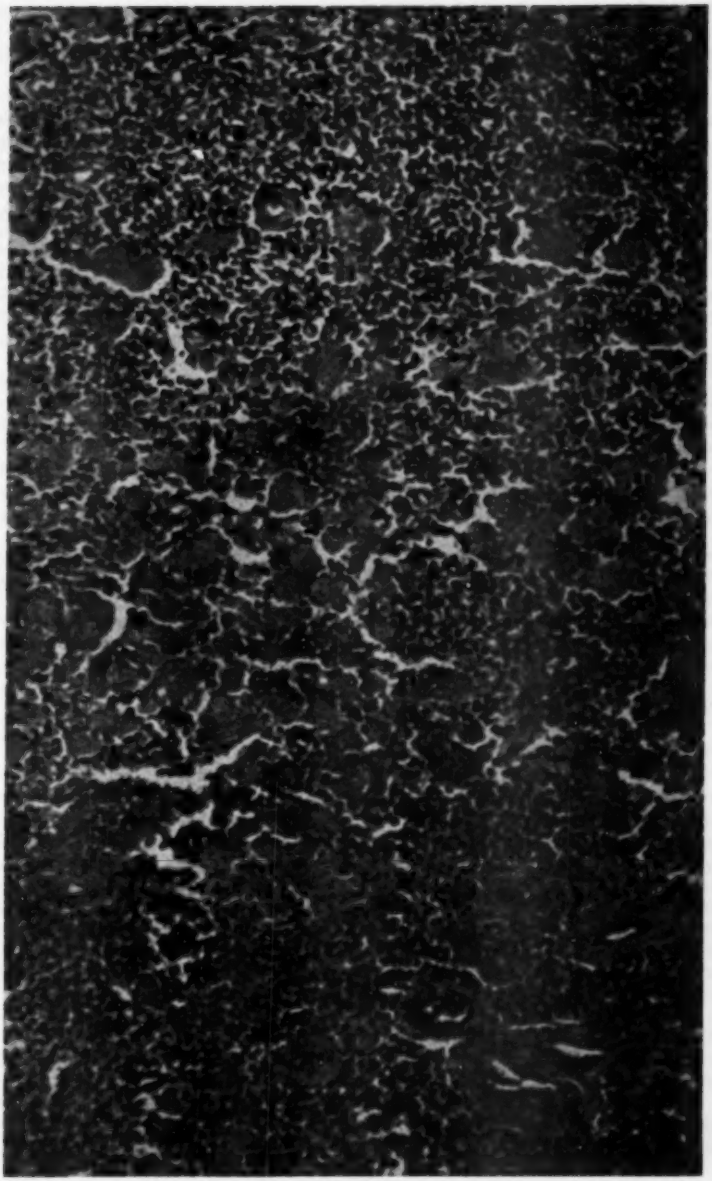

FIG. 4. Left femoral lymph node after ACTH therapy, showing marked hyaline changes.

500 c.c. of 5 per cent glucose in distilled water during a period of eight hours once daily. Circulating eosinophils, which had dropped to 55 per cubic millimeter with 80 mg. of the drug given daily intramuscularly, gradually declined to 11 per cubic millimeter with intravenous administration.

Intravenous therapy was maintained for four weeks. During the last week of intravenous therapy, the daily dose of 25 mg. Acthar-c in 500 c.c. of 5 per cent glucose in distilled water was infused slowly over a period of 12 hours.[8] There was slight further regression of the pulmonary densities. The mediastinal lymph node enlargement completely disappeared (figure 3). It was felt that the minimal residual pulmonary densities represented irreversible fibrotic changes in the lung parenchyma.

Frequent studies were performed during the eight weeks of Acthar-c therapy. The circulating eosinophils rapidly fell from an initial count of 450 per cubic millimeter to levels of between 11 and 17 per cubic millimeter. The 17-ketosteroid excretion increased from 4.5 to 25 mg. per 24 hours. The blood sodium level on a salt-free diet was maintained at an average of 140 mEq. The blood potassium level fell to 3.8 mEq. in the fourth week of therapy. The administration of potassium chloride avoided any subsequent hypopotassemia.

The serum proteins and A/G ratio, which were normal in the second hospital admission, remained at normal levels. The Mantoux test with 1.0 mg. old tuberculin was negative before and after the course of therapy. The patient gained 8 pounds during his hospital stay. Blood pressure levels remained normal throughout.

The enlarged inguinal and femoral glands noted on admission completely disappeared at the termination of treatment. One of the glands in the left femoral region which was barely palpable at the end of treatment was removed for biopsy.

Pathologic Findings (Dr. Alfred Angrist): Biopsy of femoral gland prior to treatment (figure 1): Section showed preserved follicular and sinusoidal architecture, with focal distortion by diffusely placed nodular accumulations of fairly large cells with eosinophilic cytoplasm and clear oval-shaped nuclei resembling epithelioid cells. Some of these nodules contained a centrally placed giant cell of the Langhans type. No evidence of caseation was seen in any of the sections, and no asteroid bodies were present. No marked reticuloendothelial proliferation was evident. Focal hyalinosis in lamellated tortuous parallel arrangement was present in only an occasional focus in the node, the material suggesting collagen.

Diagnosis: Femoral node: Tubercle-like structures without caseation consistent with Boeck's sarcoid.

Biopsy of femoral gland subsequent to treatment (figure 4): Sections of lymph node showed quite extensive hyalinosis in focal accumulations and merging in a confluent fashion to involve the lymph node rather diffusely and extensively. No tubercle-like structures of Boeck's sarcoid were seen in any of the sections. The hyaline material had a rather wavy pattern and was deeply and quite uniformly eosinophilic, some areas showing a less intense eosinophilic staining than others. In general, the hyaline material was distributed more extensively toward the cortex and peripherally, with sparing of the marginal sinus throughout. In one zone the capsule showed similar hyaline infiltrate, and at this focus it seemed to involve the marginal sinus minimally. The entire lymph node showed no hyperplastic changes, and generally gave the over-all impression of considerable atrophy.

Congo red and iodine stains were negative for demonstration of amyloid, none of the hyaline material showing characteristic staining affinity.

Diagnosis: Lymph node showing preservation of architecture, with atrophy and rather extensive focal and diffuse hyalinosis.

It is interesting to note that not all of the pathologic criteria for sarcoidosis which were present in the first biopsied lymph node were present in the gland removed subsequent to therapy.

Discussion

It is well known that Boeck's sarcoid may exhibit spontaneous remission. Against the likelihood that the improvement noted in this case was coincidental rather than induced by the therapy given are certain observations. Both clinically and roentgenographically, the patient showed progressive evidence of spread of pulmonary involvement during the two years of observation prior to therapy. At the time of the second admission he had definite clinical evidence of marked pulmonary inadequacy which had developed during the previous month. Study of the serial roentgenograms over the course of two years showed constant progressive involvement of the lung parenchyma and enlargement and lobulation of the mediastinal shadow. The marked clinical and roentgenographic improvement in one month during Acthar-c therapy suggests a direct and positive effect of the drug.

In view of the short interval of time which has elapsed since the termination of therapy, it is not possible to evaluate the permanence of the remission at this time. The duration of this remission will be determined by subsequent observation and study.

Although the administration of smaller increasing doses may have contributed to the ultimate result, maximal benefit occurred during the several weeks of large doses with intramuscular and intravenous Acthar-c therapy. It appears that full therapeutic effect necessitates doses of 80 mg. per day intramuscularly, or 25 mg. per day intravenously if administered slowly. It seems likely that previous reports of failure of ACTH therapy in sarcoidosis may have been due to inadequate dosage, insufficient duration of therapy, or both.

In addition to clinical and roentgenographic improvement, an attempt was made to evaluate the effect of Acthar-c therapy on lymph node pathology. With this in mind, a collection of large palpable lymph nodes in each femoral region was chosen for study. A node from the right femoral area removed prior to therapy showed unmistakable evidence of sarcoid changes. Following therapy, all of the nodes in both femoral regions regressed so that they were impalpable except for one node in the left femoral area, which was removed and sectioned.

We realize the limitations of an accurate appraisal of the pathologic changes induced by the drug when two separate lymph nodes are studied. The presence of extensive hyaline changes and the absence of sarcoid infiltration in the lymph node biopsied after therapy were striking. Similar changes have been described by Sones and his associates [4] in skin and parotid gland biopsies following cortisone therapy. We believe that the changes noted in the second lymph gland after therapy were significant.

Summary

1. A case of marked, progressive pulmonary and glandular sarcoidosis has been treated intensively with Acthar-c (ACTH).

2. Marked clinical and roentgenographic improvement was observed.

3. The pathologic changes observed in lymph nodes before and after therapy are described.

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LOWER NEPHRON NEPHROSIS: DEVELOPMENT OF HYPOKALEMIA DURING RECOVERY *

By JAMES J. CALLAWAY, M.D., and WILLIAM ROEMMICH, M.D.,
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ACUTE renal insufficiency due to lower nephron nephrosis [1] occurs in the crush syndrome,[2, 3, 4] intravascular hemolysis due to transfusion of incompatible blood [5, 6, 7] and various poisons, especially carbon tetrachloride.[8–12] Since the earlier descriptions of this syndrome by Bywaters,[3, 4] there have been many therapeutic advances. At the present time treatment is based on the maintenance of fluid, electrolyte and nitrogen balance during the period of anuria and diuresis. The "artificial kidney" holds much promise for the management of these patients, but the technical difficulty associated with its use necessitates that the majority of patients with lower nephron nephrosis be treated by more conservative methods.

This report presents pertinent data relating to potassium metabolism in a case of lower nephron nephrosis with anuria of 14 days' duration. Recent publications on lower nephron nephrosis do not mention the use of potassium in the management of these patients. On the contrary, emphasis is placed on the harm that may result from potassium administration.[14] Since it seems likely that hypokalemia may explain certain of the deaths that occur during apparent recovery, it is hoped that this report will direct attention toward its detection and management.

* Received for publication May 11, 1951.

From the Clinic of General Medicine and Experimental Therapeutics of the National Heart Institute (Cardiovascular Clinic, U. S. Marine Hospital, Baltimore), U. S. Public Health Service.

Case Report

A 19 year old Norwegian seaman was admitted April 19, 1950, following exposure to carbon tetrachloride by inhalation. During the 48 hours preceding exposure he had consumed large quantities of alcoholic beverages. Exposure to carbon tetrachloride occurred on the morning of April 17, 1950, and was followed by anorexia,

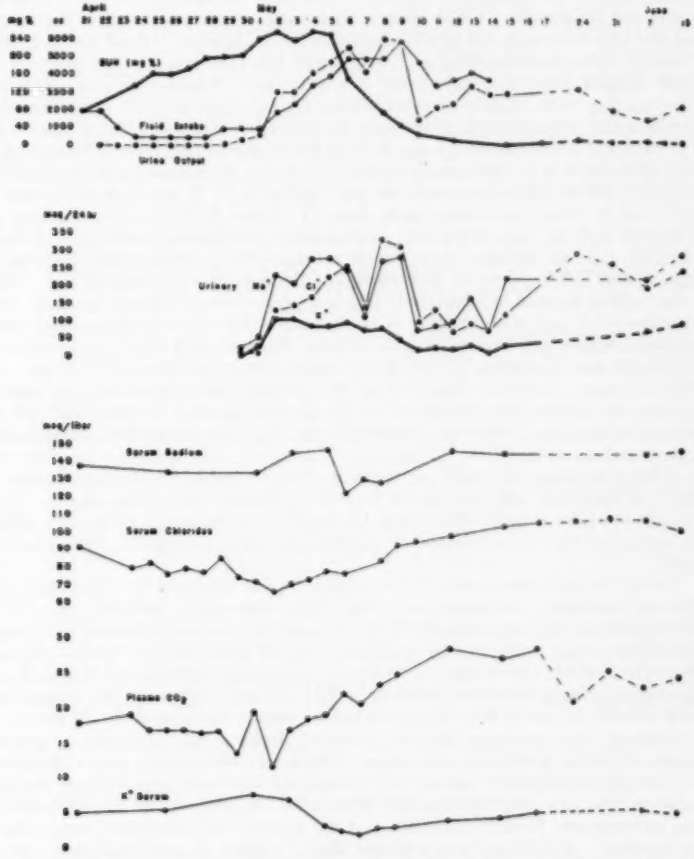

FIG. 1. Graph of fluid intake and urine output, and urinary and serum electrolytes. These observations began on April 21, 1950, five days after admission.

nausea and vomiting. On the day of admission there was severe epigastric and bilateral flank pain, with anuria of 24 hours' duration.

On admission he appeared acutely ill. Weight was 125 pounds. Temperature was 98° F., pulse 72 and blood pressure was 110/68 mm. of Hg. The conjunctivae

were icteric. Skin and mucous membranes were dry. The lungs were clear. The heart was not enlarged; there was a Grade I apical systolic murmur. The liver edge was at the costal margin and acutely tender. There was tenderness over both kidneys.

X-ray examinations revealed no evidence of pulmonary infiltration. The heart, liver and kidneys were of normal size; there were no urinary calculi. Hemoglobin was 14.5 gm. per cent; hematocrit was 48 per cent. Urine on admission showed a specific gravity of 1.010, alkaline reaction, 4 plus albumin, and numerous white blood cells and red blood cells. Blood urea nitrogen and serum and urinary electrolytes during the hospital course are graphically presented in figure 1. Total serum protein was normal throughout his illness. Total serum bilirubin was 4.6 mg. per cent on the fifth hospital day; five days later it was normal. Thymol turbidity and zinc sulfate turbidity were slightly elevated on the fifth hospital day; 13 days later they were within the normal range, where they subsequently remained. There was 56 per cent retention of bromsulfalein (5 mg./kg.) in 45 minutes on the seventh hospital day; 16 days later there was 7 per cent retention of dye, and four weeks later no retention of the dye. Prothrombin concentration was decreased to 25 per cent of normal on the fifth day of illness; with large daily doses of vitamin K, it was raised during the next 10 days to 80 per cent of normal. Subsequently, it remained in the normal range.

During the first 14 days urine output averaged 40 c.c. daily. Emesis, with an average loss of 600 c.c. vomitus daily, occurred through the fifth hospital day. After this the patient became semicomatose and vomiting ceased. Three thousand cubic centimeters of 5 per cent glucose in water and 1,000 c.c. of saline were given parenterally during the first 48 hours. During the next nine days, maintenance of fluid balance was attempted by the daily administration of 550 c.c. of 20 per cent glucose in water. Diarrhea appeared on the eleventh day, and during the ensuing three days the patient received 900 c.c. of 20 per cent glucose in water and 100 c.c. of normal saline daily. After the fourteenth day fluid and electrolyte administration was governed by urinary loss (figure 1). Coincident with the diarrhea there was loss of large amounts of blood per rectum. Twelve hundred cubic centimeters of washed red blood cells and 1,000 c.c. of fresh whole blood corrected his anemia. There was slight increase in heart size during the oliguric period but no pulmonary edema. Body weight at the end of 14 days of oliguria was three pounds less than admission weight.

During the first three weeks in the hospital he was critically ill. Five days after admission he became semistuporous. Increasing restlessness followed, and on the tenth hospital day he became totally blind. Amaurosis remained complete for 13 days, although there was never objective evidence of eye abnormality. Vision gradually improved and within two weeks was normal. On the eleventh hospital day there was a generalized convulsive seizure lasting seven minutes. Although the patient was heavily sedated following this, minor convulsive seizures continued for 72 hours.

Although diuresis began on the fourteenth hospital day, the patient remained critically ill for an additional seven days. There was intermittent stupor alternating with extreme excitement. Speech was incoherent and boisterous, and it was impossible to feed him. At this time the blood urea nitrogen was 77 mg. per cent, the serum chloride was 86 mEq. per liter, and the plasma CO_2 combining power was 21 mEq. per liter. An electrocardiogram on May 7 (figure 2) was consistent with the serum potassium of 2.42 mEq. per liter on this date. On the twenty-first hospital day 5 gm. of potassium chloride in 1,000 c.c. of normal saline were administered intravenously over an eight hour interval. Clinically there was dramatic improvement. The sensorium cleared completely and the episodes of excitement abated. Coincident with the clinical improvement, serial electrocardiograms became normal. The following day another 5 gm. of potassium chloride were given intravenously. Subsequently, a full diet was taken and the patient improved rapidly.

By the time of discharge on the fifty-eighth hospital day he was asymptomatic. Blood counts and blood and urine electrolytes were normal. The urine was acid, with a specific gravity of 1.021. The microscopic sediment was normal. Specific hepatic and renal function tests revealed no abnormality.

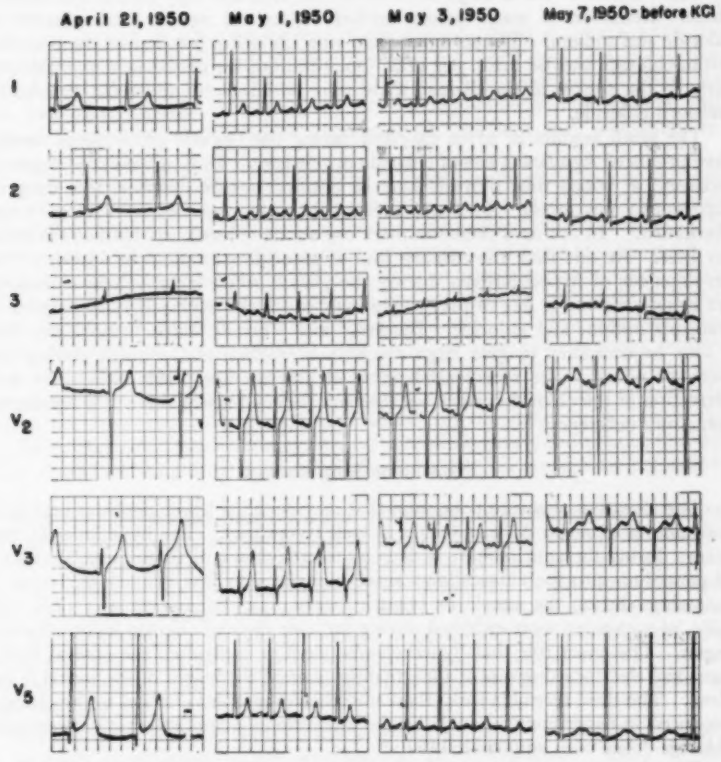

FIG. 2. Electrocardiograms showing the progressive increase in amplitude of T-waves in V_2 and V_5 and abbreviation of the Q–T interval through May 1, 1950. From May 1, 1950, through May 7, 1950, the T-waves decreased in size, the Q–T interval became prolonged, and prominent U-waves developed, suggesting hypokalemia.

DISCUSSION

The recognition that the administration of large amounts of fluid failed to relieve anuria and often produced fatal pulmonary edema [1, 15] changed the basic concepts in the treatment of lower nephron nephrosis. Limiting fluid intake to cover only water lost, as advocated by Snapper,[14] has decreased the mortality rate and increased the survival time of many of the fatal cases. During this increased survival period, profound electrolyte disturbances may occur.

The elevation of blood urea nitrogen and serum creatinine and the depression of serum chloride and plasma carbon dioxide capacity are well recognized features of the anuric stage. The depression of serum chloride is often striking. In the present case the extrarenal loss of chloride through vomiting and sweating no doubt accounts for a large amount of the chloride loss during the anuric phase. Retention of water would further reduce the serum concentration of chloride and sodium. The serum sodium was 139 mEq. per liter at the time the serum chloride was 68 mEq. per liter. In addition, Burch [16] has suggested that early in the course of the disease there may be failure of the renal tubules to reabsorb chloride.

The small amount of urine excreted during the oliguric phase could hardly have produced significant loss of chloride in this case. During the early stages of recovery, at which time diuresis may be marked, serum chloride may drop to dangerously low levels. This was seen in the cases reported by McGee [12] and Blackburn.[2] In the case presented here the serum chloride dropped to 68 mEq. per liter. At this time the urinary loss of chloride exceeded the intake. The development of hypochloremia during the period when large volumes of urine are being excreted is due in part to the inability of the damaged renal tubules to reabsorb sodium and chloride. Burwell [7] and Thorn [17] have pointed out that it may be necessary to give large amounts of sodium and chloride during the recovery phase. The recent publication of Darrow and Pratt [18] suggests that correction of the chloride deficit will be more difficult when there is a coexistent potassium deficiency.

Potassium Metabolism

The elevation of serum potassium that may occur in lower nephron nephrosis with anuria of seven days or longer is well recognized. The hyperkalemia that occurs during the anuric phase is due to the breakdown of tissue, with liberation of potassium into the extracellular space and the very low urinary excretion of potassium during the anuric or oliguric phase. In the present case only 12.5 mEq. of potassium were excreted during the nine days of oliguria before diuresis began. The exact rôle that hyperkalemia plays in explaining the clinical symptoms and electrocardiographic abnormalities seen at the height of the anuria is not clear. The close resemblance of these electrocardiographic changes to the changes produced in experimental anuria by the intravenous administration of potassium chloride [19] has been emphasized.[20, 21, 22]

The development of hypokalemia in lower nephron nephrosis has received little attention. Marquis and Schnell [23] reported a case in which death was probably due to hypokalemia following several days of intestinal irrigation. Burch,[16] in discussing the urinary findings in lower nephron nephrosis, mentions that "reducing substances are occasionally found in small amounts, and potassium and creatinine are present in abnormally large quantities." Snapper [14] points out that "rare cases have been described where, during anuria, the potassium content of the serum decreased." The present case report suggests that hypokalemia may occur during recovery and account for the delayed clinical improvement.

Failure to recognize this syndrome may be due to the following: first, electrocardiographic evidence of hypokalemia is not specific, and second, Tarail [24] has

shown that cellular deficits of potassium—as demonstrated by retention of the ion in balance studies—are usually, but not always, associated with a low serum potassium. Therefore, the two most commonly employed methods used to detect abnormalities of potassium metabolism, namely, the electrocardiogram and serum potassium determinations, may not reflect a true deficiency of potassium.

In the present case the persistence of the critical illness at a time when the urea nitrogen had fallen from 265 mg. per cent to 77 mg. per cent, the serum chloride was 86 mEq. per liter and the CO_2 combining power was 21 mEq. per liter was most difficult to explain. The dramatic clinical improvement that followed potassium administration supported the evidence that potassium deficiency was present.

In the study of transfers of potassium in renal insufficiency, Elkinton [25] has shown that in most cases in which the ion accumulated in the extracellular phase the cellular decrement was at least as great as the extracellular increment. "If the transfers of intracellular potassium are arbitrarily subdivided into those which move with nitrogen according to cell anabolism or catabolism, and those which enter or leave intact cells, the data indicate that in only two cases did part or all of the potassium from catabolized cells enter intact cells." [25] The possibility that intact cells will store potassium during the period of hyperkalemia seems remote. Therefore, when the serum potassium falls during the recovery phase, any anabolic demand for potassium in the absence of potassium intake can only be met by the development of potassium deficiency by the intact cells. Thus, the possibility that an intracellular deficiency of potassium may develop once diuresis starts should be suggested by the hyperkalemia that occurs during the anuric phase.

Data from the present case (figure 1) reveal that large amounts of potassium may be lost in the urine during the initial stages of diuresis. From the onset of diuresis until potassium chloride was administered, a total of 489 mEq. (19.1 gm.) of potassium was lost in the urine. Even during the period when potassium chloride was administered parenterally there was a negative balance of potassium. The data indicate that potassium salts might possibly have been administered over a longer period; however, by the third day of parenteral administration of these salts the patient was able to take a regular diet estimated to contain 50 mEq. of potassium per day.

Factors other than excessive urinary loss of potassium in the initial stages of recovery contributed to the development of hypokalemia. Early in the oliguric phase there was vomiting with loss of potassium. Later the ingestion of potassium-containing food was delayed by his semicomatose state.

Electrocardiographic Changes

The electrocardiographic changes of hyperkalemia were demonstrated by the present case (figures 2 and 3). The changes consisted primarily of tall peaked T-waves and abbreviated Q-T interval. These changes were most marked on May 1, 1950, at which time the serum potassium was 7.55 mEq. per liter. During the interval of increasing urinary output, from May 1 to May 7, there was a progressive decrease in the size of the T-waves in all leads and the development of tall U-waves, best seen in Leads V_2 and V_3. These changes were most marked

on May 7, when the serum potassium was 2.4 mEq. per liter. Following the administration of potassium chloride the T-waves increased in amplitude and the U-waves decreased in size (figure 3). By May 11 the U-waves were very small. Electrocardiographic tracings subsequent to May 16 showed no essential changes.

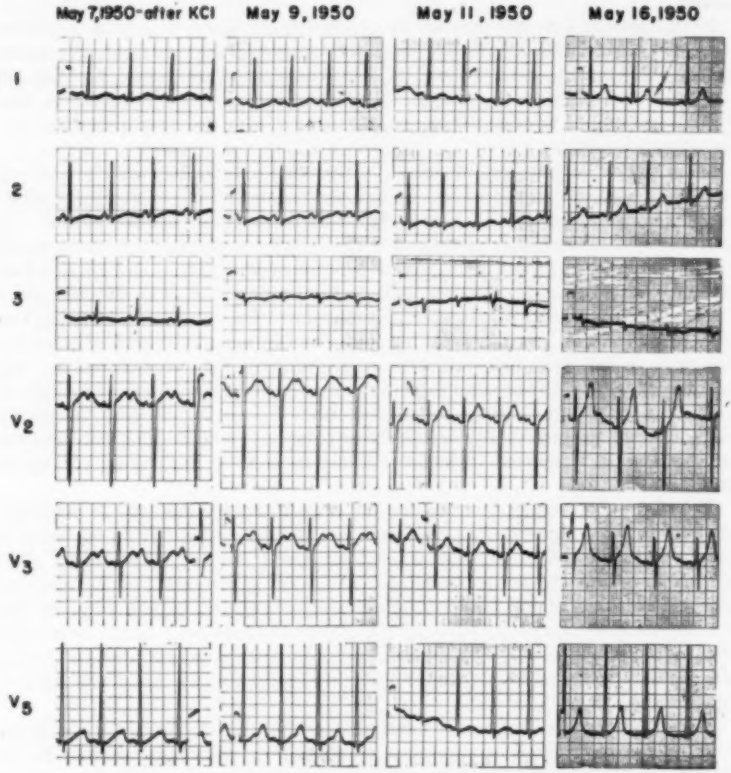

FIG. 3. On May 7, 1950, immediately following potassium chloride administration, the T-waves showed increased amplitude, the U-waves were less prominent, and the Q-T interval was shortened. Tracings on May 9, 11 and 16, 1950, show reversion to normal.

Reports regarding electrocardiographic evidence of hypokalemia have stressed lowering of the T-waves and lengthening of the Q-T interval. These changes have been seen primarily in cases of familial periodic paralysis,[26, 27] nephritis [28] and Addison's disease treated with desoxycorticosterone acetate.[29] In none of these reports has the occurrence of U-waves been stressed. Ellis,[30] in reporting on the electrocardiogram seen in severe malnutrition, mentions the occurrence

of U-waves and speculates whether they may be due to low serum potassium. In the recent report of Bellet et al.,[81] U-waves were present in 53 per cent of the cases of hypopotassemia. They found that U-waves were most common and prominent in those patients with vomiting, colitis or diarrhea, and were less frequent and prominent in diabetics being treated for diabetic coma. Their speculation that the development of prominent U-waves might be related to the rapidity of development of hypokalemia appears to apply to the present case, in which there was rapid loss of a large quantity of potassium.

Treatment

Strict limitation of fluid intake during the oliguric phase of lower nephron nephrosis is essential for the prevention of pulmonary edema, and in general is the accepted method of treatment.

During the recovery phase it has been recommended that fluid intake be adequate to cover urinary output and insensible fluid loss. If the patient is edematous, part of the urine excreted at this time represents the correction of hypervolemia, and moderate limitation of fluid intake when the serum creatinine and blood urea nitrogen are returning to normal appears more appropriate and may prevent the loss of essential electrolytes that might occur with excessive urinary output.

It has been pointed out previously that large amounts of sodium and chloride may be required during recovery.[7, 17] The present report indicates that potassium deficiency may likewise develop during the recovery period. If an adequate diet with average potassium content can be eaten during the period when urine output is being reëstablished, the development of potassium deficiency is more remote. However, if potassium deficiency should occur, it would appear necessary to administer potassium salts for its prompt correction. If the clinical condition of the patient prevents the oral administration of potassium salts, parenteral administration appears justified.

Summary and Conclusions

A case report of lower nephron nephrosis with the development of hypokalemia during the recovery phase is presented. The mechanism of development of hypokalemia, the electrocardiographic findings and therapy are discussed. The prompt recognition and management of hypokalemia which may occur during recovery may prevent some of the late deaths that have been seen in lower nephron nephrosis.

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ACQUIRED COARCTATION IN THE NEW CHANNEL OF A HEALED DISSECTING AORTIC ANEURYSM *

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The volume of literature concerning dissecting aneurysm of the aorta has become so great since Shennan's monograph in 1934 [1] that only an unusual case seems to warrant recording. In the one to be presented, a coarctation developed following a "double barreled" transformation of the aorta from its ring to bifurcation.

Case Report

A 39 year old single white female office worker had enjoyed good health until November 27, 1945, when, while working at her desk, she suffered a sudden onset of constantly boring pain radiating from the tip of her sternum through to her back. This occurred at a time when she was severely exhausted from overwork. A physician saw her immediately, and later informed her father that individuals with this type of "heart condition" seldom live beyond the age of 50. No further details relative to this examination are known. The pain became worse and, in association with it, the patient observed pulsations in her neck. Five days after onset the pain had become so severe that she was admitted to another hospital. Anorexia, nausea and vomiting on several occasions, restlessness and a minimal cough were the only additional features. On examination the jugular veins were distended bilaterally but were nonpulsating, while the carotid arteries were strongly pulsating in a "leaping" manner. More important, there was heard over the entire chest, anteriorly and posteriorly, a blowing, continuous to-and-fro murmur. The systolic component was best heard over the apex, and the diastolic component over the third left and second right intercostal spaces. The heart was enlarged to just beyond the left nipple line, and there was a pericardial friction rub along the left border of the sternum. Blood pressure in the right arm was 136 mm. mercury systolic and 58 mm. diastolic; in the left arm, 144 mm. mercury systolic and 56 mm. diastolic. The heart rate was regular, and varied from 120 upon admission to 90 at the time of discharge. An electrocardiogram was essentially normal. A portable chest x-ray revealed a possible mediastinal tumor, but barium swallow showed the esophagus to be in its normal position by fluoroscopy. With the exception of a trace of albumin the urine examination was normal. The white blood count was 11,700, the sedimentation rate 41 mm. at the end of one hour, and the blood Kahn test negative. The oral temperature was 102.2° F. on admission and gradually subsided to normal. At the time of discharge, five days later, the pain had disappeared. The only record of a previous physical examination available for comparison was made in 1941. At that time, other than an acute cellulitis of the neck, examination was essentially normal, and the blood pressure was 126 mm. mercury systolic and 76 mm. diastolic.

The patient recovered and was able to resume work. She noticed during the next four and one-half years a gradually increasing irritability, dyspnea on moderate exertion, and difficulty in swallowing the more solid foods. The pulsations in her neck became more marked during this interval. She was treated for hyperthyroidism with heart failure, receiving Lugol's solution, thiouracil, digitoxin and barbiturates

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upon different occasions, without success. Two basal metabolic rates were plus 22 and plus 29.

About one month prior to admission to the Evanston Hospital on May 19, 1951, the patient noticed, while dining, a sudden onset of severe palpitation and tachycardia. This attack persisted for about 12 hours; thereafter, similar spells occurred frequently, with associated increase in severity of cervical pulsations and dyspnea. The latter increased rapidly until it was present at bed-rest.

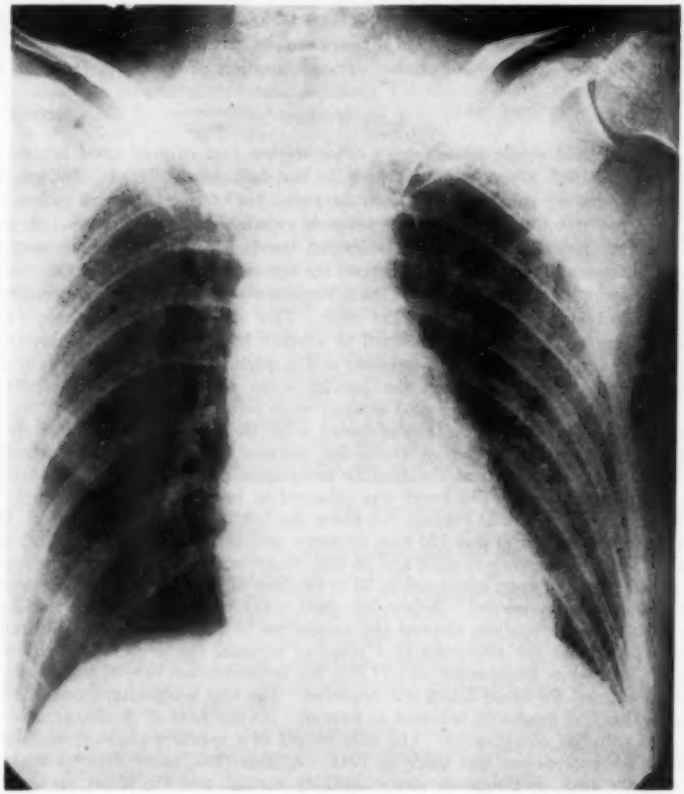

FIG. 1. Posteroanterior x-ray of the heart one week after onset in 1945.

Upon admission the patient was in acute heart failure. There were visible pulsations over the lateral and anterior surfaces of the neck; the entire chest presented a heaving, turbulent appearance. Systolic and diastolic thrills were palpable over the entire chest and were associated with a very loud to-and-fro murmur, best heard over the base of the heart. The heart was markedly enlarged to both the right and left. Resonance was impaired over the lung bases posteriorly and in the axillae, with coarse râles throughout both lung fields. The liver extended to the umbilicus and

was tender. No sacral or ankle edema was present. The brachial blood pressure was 140 mm. mercury systolic and 80 mm. diastolic; respirations, 36; pulse, 110 and regular; and oral temperature, 98.6° F.

Intravenous aminophylline, oxygen, sedation and digitalization achieved considerable improvement initially and for the first few days; thereafter, all measures failed to check the severe decompensation. Six days after admission auricular fibrillation developed; the brachial blood pressure at this time was 178 mm. mercury systolic and 50–0 mm. diastolic. Blood Wassermann, Kline and Kahn tests were negative; plasma non-protein nitrogen values increased from 72 to 144 mg. per cent;

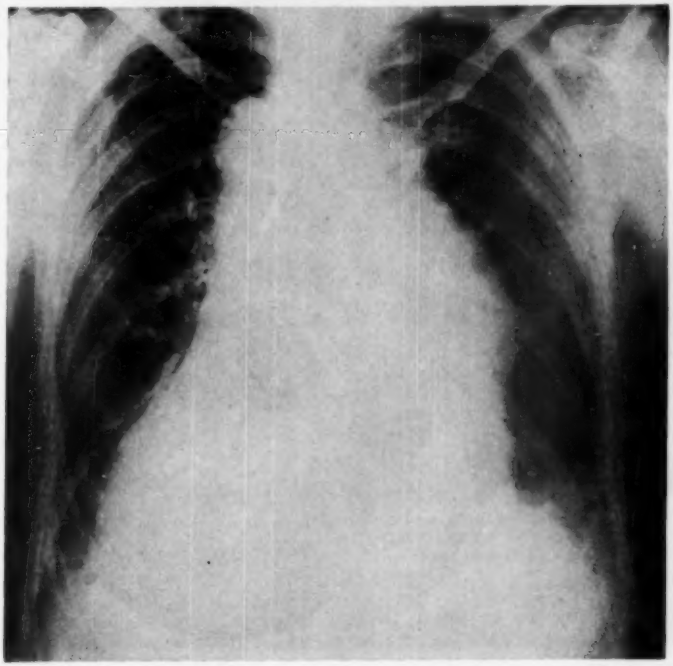

FIG. 2. Posteroanterior x-ray of the heart during the present admission.

the values for blood plasma chlorides were 621 mg. per cent; those for blood sugar, cholesterol, calcium, albumin and globulin were normal. Other laboratory determinations were compatible with cardiac decompensation. A single blood culture was negative. The electrocardiogram revealed left heart strain with digitalis effect and later confirmed the auricular fibrillation without other significant change.

Posteroanterior, right, and left anterior oblique x-rays of the heart and great vessels along with fluoroscopy revealed the following picture. There was a localized bulge in the upper half of the right heart border. Cardiac contractions along the left border were vigorous and irregular; those over the lower half of the right border were less vigorous. The retrosternal space was almost completely filled with heart

shadow. The aortic shadow was widened in the ascending portion and arch; in the upper portion of the descending aorta and distal portion of the arch was an apparent local fusiform aneurysmal dilatation. The esophagus was markedly deviated posteriorly and to the left. Figure 1 shows an anteroposterior view of the heart one week after onset in 1945, and figure 2 a similar view taken during the present admission.

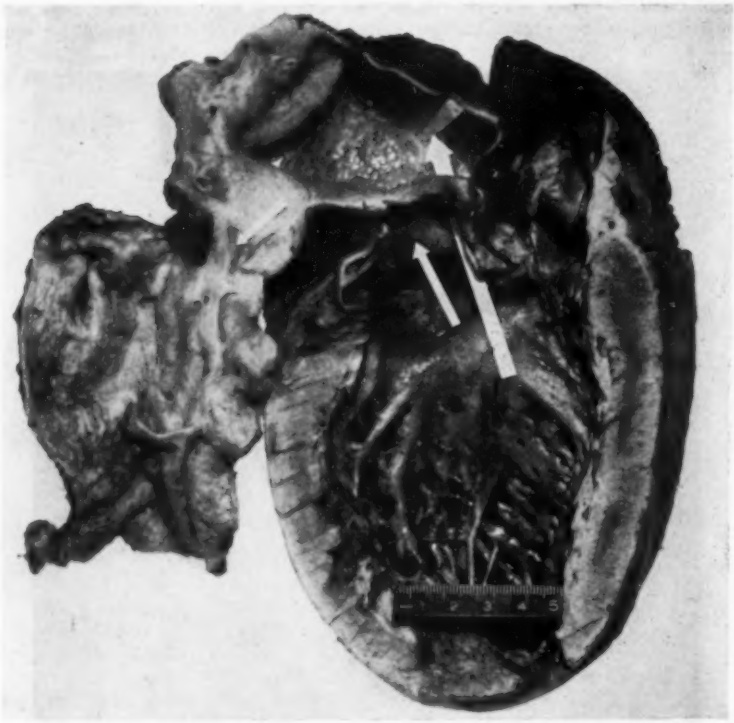

FIG. 3. The arrow on the left points to the coarctation of the dissected channel. The middle arrow points to the opening of the original channel. This channel is not opened and courses posteriorly to the dissected channel. The arrow on the right goes through the intimal tear into the dilated portion of the dissected channel.

The patient's condition became rapidly worse and she died on June 9 while being helped off a bedpan.

Necropsy Findings: The body weighed an estimated 64 kg. and was 192 cm. long. There were cyanosis and marked distention of the cervical veins. Minimal bilateral hydrothorax and marked passive congestion of the lungs, liver, spleen and kidneys were present. There was no dependent edema. A lobular pneumonia was present in all lobes.

The heart weighed 955 gm. The aortic ring was 13.0 cm. in circumference and

the valve cusps were fenestrated. A transverse rent at the aortic ring in the posterior sinus of Valsalva through the intima and inner portion of the media, measuring 1 cm. in length, led into the spurious channel of a dissecting aneurysm. The dissection extended from the aortic ring to the bifurcation of the common iliacs, giving the entire aorta a "double barreled" appearance, the "septum" between being formed by the intima and a part of the media. The new channel occupied a right lateral and posterior position in its course to the common iliacs. The thoracic aorta was dilated throughout, most markedly in the ascending portion and arch, measuring 7.5 cm. in diameter in its widest portion and tapering to 2.5 cm. in diameter at the diaphragm. This aneurysmal dilatation had caused an erosion on the left side of the vertebral bodies in this area. The new channel was much larger than the original one, which measured slightly less than 4 cm. in circumference throughout its thoracic portion. At the level of the left subclavian artery the new channel was constricted to 3 cm. in circumference, whereas immediately beyond this point it ballooned out to a circumference of 9 cm. By its pressure upon the true lumen and its own constriction at the

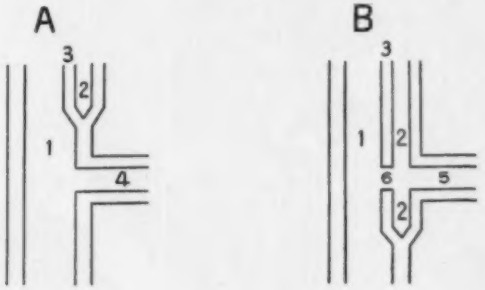

FIG. 4.

1. Aortic channel.
2. Newly dissected channel.
3. "Septum" between aortic channel and dissected channel.
4. Artery coming from main aortic channel.
5. Artery coming from new channel after dissection.
6. Hole left in "septum."

level of the left subclavian artery, an acquired coarctation was effected (figure 3). This resulted in dilatation of the intercostal arteries, with erosion of the posterior second to eighth ribs bilaterally.

There were a few atheromatous plaques in both channels of the ascending aorta. In the descending and abdominal portions the new passage was studded with these plaques; a few were present in the old passage.

The left common carotid, left subclavian, coeliac, superior mesenteric, right renal and right common iliac arteries came off the old channel; the innominate, left renal (two) and left common iliac arteries came off the new channel; however, there was a corresponding hole through the "septum" into the old channel at the origin of each (figure 4).

Microscopically, the aorta showed a marked degree of medial degeneration, with loss of muscle and elastic tissue. Cleftlike spaces filled with mucoid material remained (figure 5). These changes were most marked in the arch and ascending portions of the aorta. Other sections showed dilated vasa vasorum (figure 6).

An attempt to reconstruct the pathogenesis from the necropsy findings would suggest that, following the dissection, the new channel of the ascending aorta and arch became markedly dilated as a result of destruction and loss of muscle and

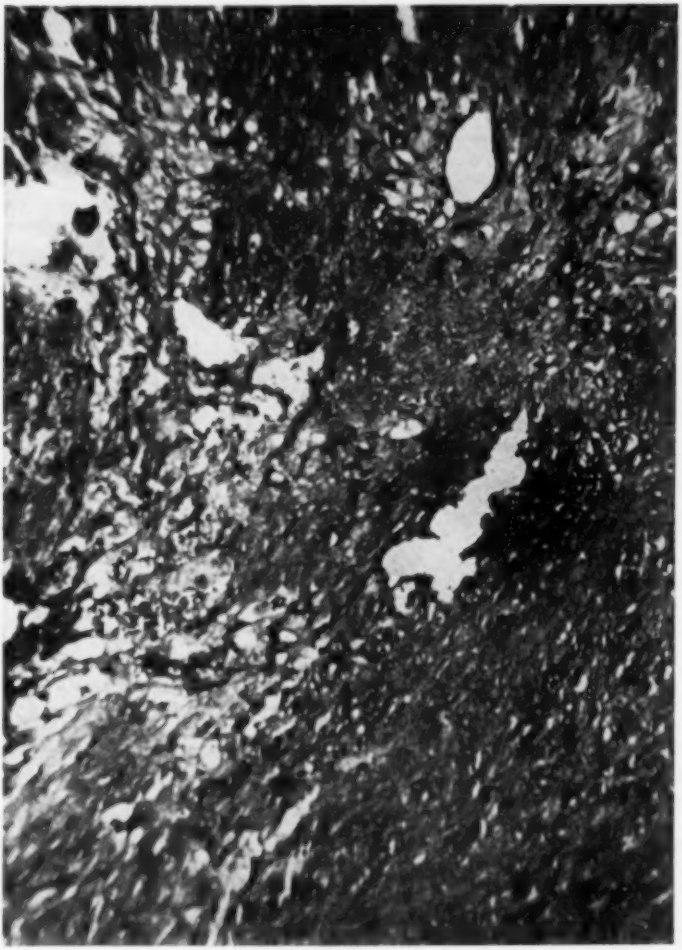

FIG. 5. Cystic spaces in the aortic media.

elastic tissue from the media. The pressure of this dilated section upon the original channel reduced the blood flow and size of the latter, thus establishing the main blood transport in the new channel. The more severe arteriosclerotic

FIG. 6. Dilated vasa vasorum in the aortic media.

changes within its walls suggest its rôle as the main channel. Stenosis of the original channel was not found at necropsy, so the stenotic area at the level of the left subclavian artery in the secondary channel was an "acquired" coarctation and resulted in dilatation of the intercostal arteries and erosion of the ribs. As the collateral circulation increased, the vessels about the neck and chest were seen to enlarge and pulsate. Of interest clinically, the patient did not exhibit signs of ischemia of any part of the body at the time of the dissection, though a

great change in blood transportation evolved, with major vessels coming from both the old and the new channels.

Discussion

As early as 1761 Nicholls described a dissecting aneurysm found at the necropsy of King George II of England. However, the term "dissecting aneurysm" was first used by Laennec in 1819. In 1838 Pennock [2] reported the first American case, and the first correct antemortem diagnosis is credited to Swaine in 1856.[3]

The incidence varies from one in every 200 autopsies, reported by Weiss,[4] to one in every 714 autopsies, reported by Flaxman.[5] The male to female ratio is 2:1 to 3:1. Schnitker and Bayer [6] found that 24 per cent in a review of 580 cases were below the age of 40. This is interesting when it is generally considered that dissecting aneurysm occurs in the fifth to seventh decades. Both extremes in age have been reported, from a boy of 14 months to a woman of nearly 100.[7]

Trauma, once considered to play an essential etiologic rôle, is not an important factor. At present a triad of predisposing factors is most commonly associated with this entity: hypertension, arteriosclerosis and medial degeneration or necrosis. Of these, hypertension has lost much of its former significance.[6, 8, 9, 10] Schnitker and Bayer,[6] in a review of 141 cases under the age of 40, reported that only about half had hypertension. Arteriosclerosis, though frequently seen in dissecting aneurysm, has little to support its rôle as an important predisposing factor.[11, 12, 13] Most dissections occur in the ascending aorta, the segment of aorta where atheromas are least frequent. Seldom does a rupture occur through a plaque; when this does occur, it is usually coincident with an overlying medical defect. The latter is seen in most cases of dissecting aneurysm.[10, 12, 14, 15, 16]

In 1930, Erdheim [31] described the medial defect as "medionecrosis aortae idiopathica cystica." He believed the disease started as an abnormal accumulation of mucoid material in the media. As this increased and spread outside interlamellar spaces, with dissolution of the previously normal muscle, collagen and elastic tissue, mucoid filled spaces were left.

Gsell [32] described a form of medial degeneration which began as focal necrosis of muscle. Disintegration of elastic tissue and collagen followed, with resultant cyst formation. Characteristically, there is a lack of inflammatory reaction, and healing, when it occurs, is by loose scar formation. Various investigators describe the medial defect in slightly varying versions, and it undoubtedly does have different forms. Sailer [7] states that "no single morbid process or causative agent can be demonstrated as consistently producing the vascular changes leading to dissecting aneurysm."

The cause of medial degeneration is unknown. Schlichter [10] is of the opinion that alteration in the vasa vasorum, with resultant tissue anoxia, is the most important factor. In 200 cases of coarctation of the aorta, reviewed by Hamilton and Abbott,[20] 22 cases of dissecting aneurysm of the aorta were found. Of 13 studied microscopically, all but one showed some degree of medial degeneration. They consider the medial defect as possibly congenital in nature, as it was associated with a congenital bicuspid aortic valve in over 50 per cent of the cases, as well as with the coarctation. Of 49 females in the series of Schnitker and Bayer,[6]

24 (48 per cent) occurred in association with pregnancy. They suggest that altered blood lipids may be a contributing factor.

Medial degeneration, however, does not always lead to dissecting aneurysm. In a study of 210 aortas from routine autopsy material, Rottino found 95 exhibiting medial changes, though nearly all were minimal.[29]

The dissection is initiated in the defective media by a hematoma which has developed from ruptured vasa vasorum. This usually breaks through the intima into the lumen of the vessel. Blood may now enter and extend the dissection. In support of this view are cases of dissecting aneurysm in which no intimal tear could be found.[8, 9, 17]

Syphilis, so closely related to saccular aneurysm, has no relation to dissecting aneurysm, and when the two are associated it is coincidental.

The usual clinical course is death within a few hours to a few days, resulting from rupture through the remaining aortic wall into the thoracic or pericardial cavities. Approximately 10 per cent of dissections, however, proceed to heal; half of these usually develop another dissection and die, whereas the other half die in cardiac failure. Some, of course, escape both fates and die of unrelated causes. The diagnosis of a "chronic" case is frequently difficult. Usually a history of pain can be elicited, though silent dissections do occur.[18, 19, 20, 21, 22] The appearance of a diastolic murmur as cardiac insufficiency develops is significant,[5] and some consider this the most important single diagnostic feature. These findings frequently lead to the erroneous diagnosis of syphilitic aortic disease. Gouley and Anderson [23] reported three cases of healed dissecting aneurysm which closely resembled this. Aortic insufficiency seldom if ever develops if the dissection has occurred beyond the arch of the aorta.[23]

The aortic diastolic murmur may be brought about by any one of several mechanisms. In our case, as in many others,[18, 27, 28] the mechanism appeared to be simply mechanical, resulting from a marked dilatation of the aortic ring. Another proposed mechanism, when the rupture is above a commissure, is the lowering of that section of the aortic cusp, thus making an incomplete closure. Several authors report such cases in which the aortic rings were of normal size.[25, 26] Resnick and Keefer,[24] in view of a normal aortic ring in their case, thought the insufficiency resulted from blood leaking into the false channel from the aorta, the mechanism being the same as in an arteriovenous fistula.

Summary

A case is reported of healed "double barreled" aorta in a 39 year old normotensive female in whom the acute dissection occurred four and one-half years prior to death. The unusual feature of this case was the presence of an acquired coarctation of the new channel, with dilatation of the intercostal and other collateral vessels and erosion of the ribs.

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SARCOIDOSIS WITH THROMBOCYTOPENIA: REPORT OF A CASE *

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ALTHOUGH involvement of the spleen in sarcoidosis is relatively common,[1] concomitant occurrence of splenic thrombocytopenia has not been widely noted. Recently, Partenheimer and Meredith [2] reported a case of splenomegaly and neutropenia occurring in sarcoidosis which was relieved by splenectomy, and referred to six additional cases in the literature. Dameshek,[3] in a review of hypersplenism, presented a case of splenic pancytopenia with nonhemolytic anemia secondary to the splenomegaly of sarcoidosis in which all the blood elements, including platelets, were depressed prior to splenectomy and elevated thereafter. Kunkel and Yesner [4] were able to collect from the literature seven cases of sarcoid granulomata of the spleen associated with thrombocytopenic purpura, and reported a case of their own in which splenectomy reversed the process. In a recent review of 110 cases of thrombocytopenic purpura for the purpose of evaluating splenomegaly, Ehrlich and Schwartz [5] reported one case associated with sarcoidosis in which splenectomy caused a favorable platelet response. Cattell and Wilson [6] reported two similar cases, both of which responded to splenectomy. Wright, Doan, Bouroncle, and Zollinger [9] have added an additional case of successful splenectomy in a four year old male, the clinical diagnosis being that of thrombocytopenic purpura, sarcoid being confirmed by pathologic examination of the excised spleen.

It would seem that the splenomegaly of sarcoidosis is usually asymptomatic, but that when it is accompanied by hypersplenism a depression of one or all of the cellular elements of the blood may result, and, as in idiopathic splenic neutropenia, splenectomy may be expected to reverse the process.

The following case is presented as one of generalized sarcoidosis associated with splenomegaly and thrombocytopenia, in which the clinical course terminated fatally before splenectomy could be performed.

CASE REPORT

A 15 year old white female was admitted to the Lutheran Hospital of Maryland on December 9, 1950, because of bleeding from the nose and mouth of 24 hours' duration.

She had suffered scant epistaxes over a two year period, these occurring once or twice a week. One week prior to admission she developed a rash on her arms and was given pills for a "blood condition." The night preceding her admission her nose began to bleed profusely, and she was seen in the accident room of another hospital, where her nose was packed. Bleeding continued as an ooze, and on the morning of admission her gums also began to bleed. She was subsequently referred to this hospital for admission as a hematologic problem.

The patient had been a premature child, weighing four and one-half pounds at birth. When she was six weeks old she had "inflamed eyes," and her parents were

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informed that she might become blind. Thereafter she was well until three years before admission when, at the age of 12, she developed "pink eye" and was sent home from school. She was studied in another hospital, where a careful examination of the eyes was made. The conjunctivae were described as red and inflamed, and there was moderate pericorneal injection. Examination of the anterior chamber of the left eye showed five black dots on the anterior surface of the lens, presumably the sites of ruptured synechiae. The media were slightly hazy, the fundi clear. Some papilledema was present. The diagnosis was iritis. The patient had a negative cutaneous tuberculin test up to 0.1 mg. dilution. Chest x-ray showed a rounded density in the right hilum, considered to be an adenopathy. The temperature was 100° F.; the blood pressure, 120/78 mm. of Hg. There was slight generalized glandular enlargement, particularly in the anterior cervical and in the inguinal regions. The spleen was palpable two fingerbreadths below the left costal margin and was described as "stony-hard." The liver was not palpable. Hemoglobin was 12.5 gm. (Sahli); white blood cells numbered 9,200 per cubic millimeter, with 60 per cent polymorphonuclears. Total serum protein was 5.39 gm., with an albumin-globulin ratio of 2.02. Blood non-protein nitrogen, calcium, phosphorus, alkaline phosphatase and cholesterol were normal. The urine was essentially normal. X-rays of the hands and feet were interpreted as normal. An axillary lymph node was then removed, and a diagnosis of sarcoidosis was made.

The patient was followed for a year in an eye clinic. Her vision became progressively impaired and extensive corneal changes were noted. She was then admitted to a local institution for the blind, where for two years she did well and was apparently free of symptoms, other than nosebleeds. She was in the expected grade of school for her age.

Physical Examination: On admission to this hospital, the patient had a temperature of 101.8° F., pulse rate of 120, respiratory rate of 22, and blood pressure of 100/60 mm. of Hg. The patient was small but well developed and fairly well nourished. There was active bleeding from the nose and mouth.

The skin was extremely pale, and numerous purpuric and petechial lesions were present, mainly on the legs. The eyes showed several corneal opacities, and there was a small subconjunctival hemorrhage on the left. The mouth and nares were filled with dark crusts, from under which fresh blood oozed. The lips and soft palate were studded with purpuric lesions. The lungs and heart were not remarkable save for tachycardia. The liver was palpable one fingerbreadth below the left costal margin and was firm. There was moderate generalized lymphadenopathy. There was pain on flexion of the right hip.

Laboratory studies showed a hemoglobin of 65 per cent of normal, sedimentation rate of 36 mm. (corrected), a packed-cell-volume of 33 cu. mm., mean-corpuscular-hemoglobin of 24 per cent, mean-corpuscular-hemoglobin-concentration of 30 per cent. The white blood cell count was 6,500 per cubic millimeter, with a normal differential pattern. There was a complete absence of platelets. The urine was grossly bloody, had a specific gravity of 1.020 and contained 1 plus albumin. A capillary fragility tourniquet test was strongly positive (30 petechiae per square centimeter). The bleeding time was 4 minutes, coagulation time (Lee-White) 10 minutes. Blood urea was 68.4 mg. per cent; blood urea nitrogen, 32 mg. per cent; serology, negative. Total serum protein was 6.6 gm. per cent, with an albumin-globulin ratio of 1.27. Blood calcium was 8.9 mg. per cent; phosphorus, 3.9 mg. per cent; van den Bergh's reaction, 0.4 mg. direct, 1.1 mg. indirect. Thymol turbidity was 9 units. The stool showed 4 plus occult blood. A sternal marrow aspiration showed slight erythroid hyperplasia. The megakaryocytes were large and numerous, but their cell membranes were intact, and neither fragmentation nor any platelet formation could be seen (figure 1). A chest x-ray showed gross enlargement of the hilar shadows in the

right upper mediastinum. There was no evidence of pulmonary involvement. A flat plate of the abdomen and pelvis showed some enlargement of the splenic shadow. Bones of the hands and feet were normal.

Transfusions of fresh whole blood from compatible donors, synthetic vitamin K intravenously, Rutin, ascorbic acid and penicillin were administered. Bleeding con-

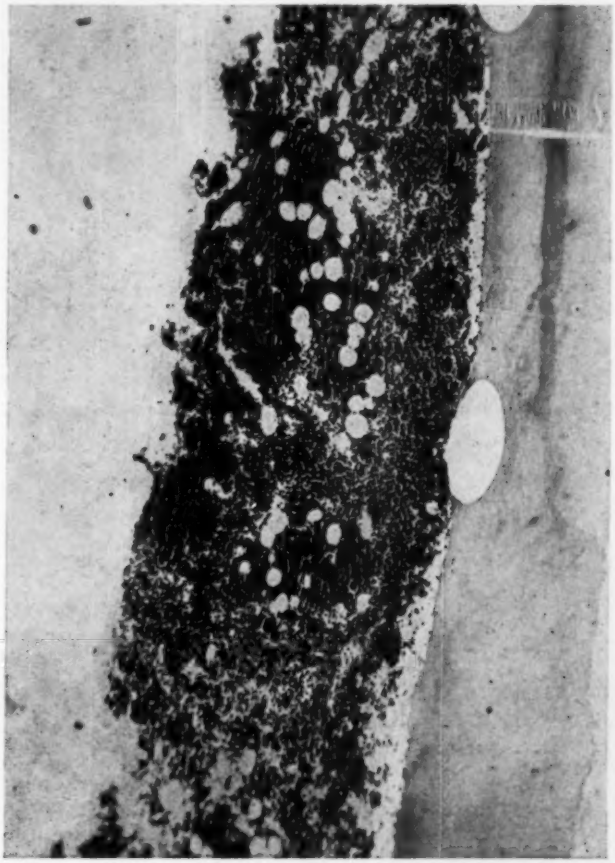

FIG. 1. Bone marrow, showing numerous megakaryocytes. Microscopically, they were seen to have intact cell membranes, and no fragmentation of platelets was present.

tinued intermittently from the nose and mouth, and steadily from the intestinal and urinary tracts, and vaginal bleeding occurred for the first time. Emesis of coffee-ground material was frequent. With transfusions, the hemoglobin rose to a high of 84 per cent. The coagulation time continued to be normal, but the bleeding time

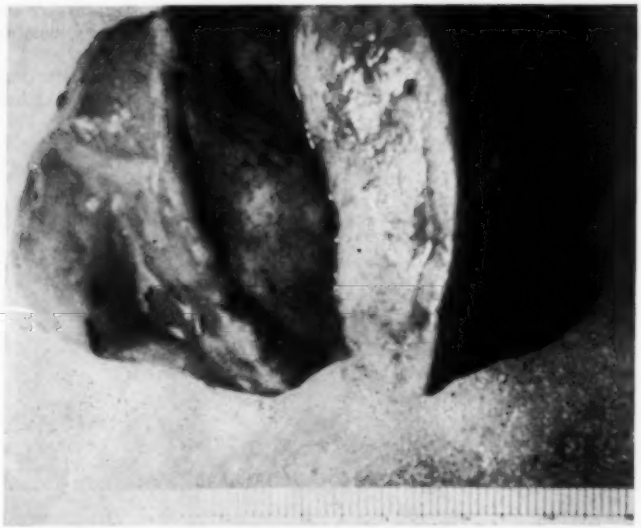

FIG. 2. Lymph node from the mediastinum, showing the edematous, everted cut surface and congestion.

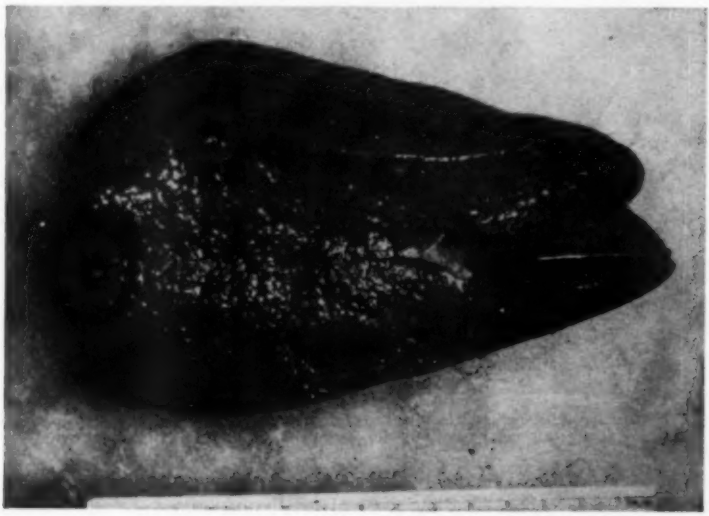

FIG. 3. Spleen, weighing 210 gm., presenting a coarsely granular, congested surface, and on section prominent small granulomatous areas.

became somewhat prolonged (18 to 20 minutes). The temperature varied between 100° and 102° F. (rectally), the pulse from 100 to 120 per minute, the blood pressure from 90 to 110 systolic over 60 to 70 diastolic.

Plans were being made for a splenectomy when, on the morning of the sixth hospital day, the patient suddenly developed generalized convulsions, lapsed into coma, and died four hours later. An electrocardiogram taken terminally showed a supraventricular tachycardia of 176 beats per minute, and evidence of coronary insufficiency.

Autopsy Findings: Significant external findings were a generalized shotty lymphadenopathy, multiple purpuric areas, and petechiae over the skin, especially of the

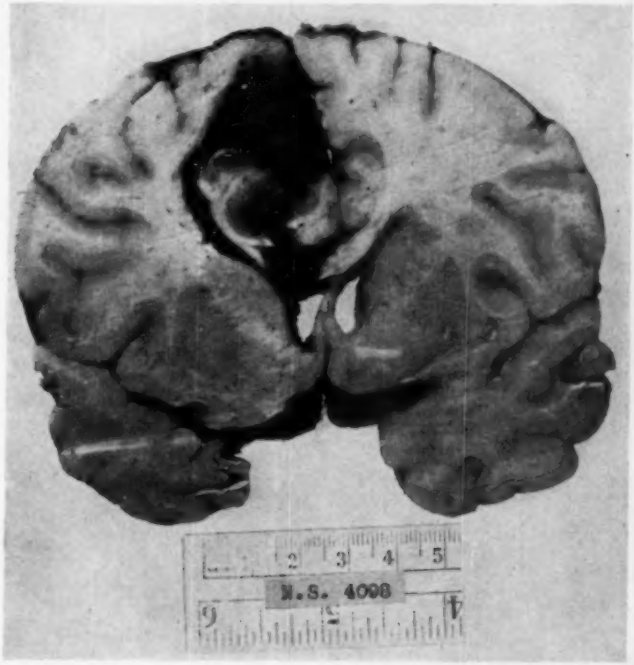

FIG. 4. Brain, coronal section, showing a large hemorrhage in the left frontal lobe, rupturing into the corpus callosum and the left ventricle.

extremities, marked pallor, and evidence of hemorrhage from nose, mouth, vagina and rectum.

The serous cavities and the serosal surfaces of all viscera were freely sprinkled with petechiae varying from pin-point size to 2 mm. in diameter. They were especially prominent in the lower lobes of both lungs, the epicardium and the small intestine. A large retroperitoneal hemorrhage had occurred in the right colic gutter.

The thymus was enlarged (15 gm.) and overlaid a mass of hypertrophied mediastinal lymph nodes, the largest of which measured 6 cm. in length and 4 cm. in

diameter. Their total weight was 180 gm. These nodes were soft and pinkish-white. Their cut surfaces were uniform but congested (figure 2).

The liver weighed 2,500 gm. and was light brownish-red in color and somewhat soft in consistency. Its cut surface showed some congestion.

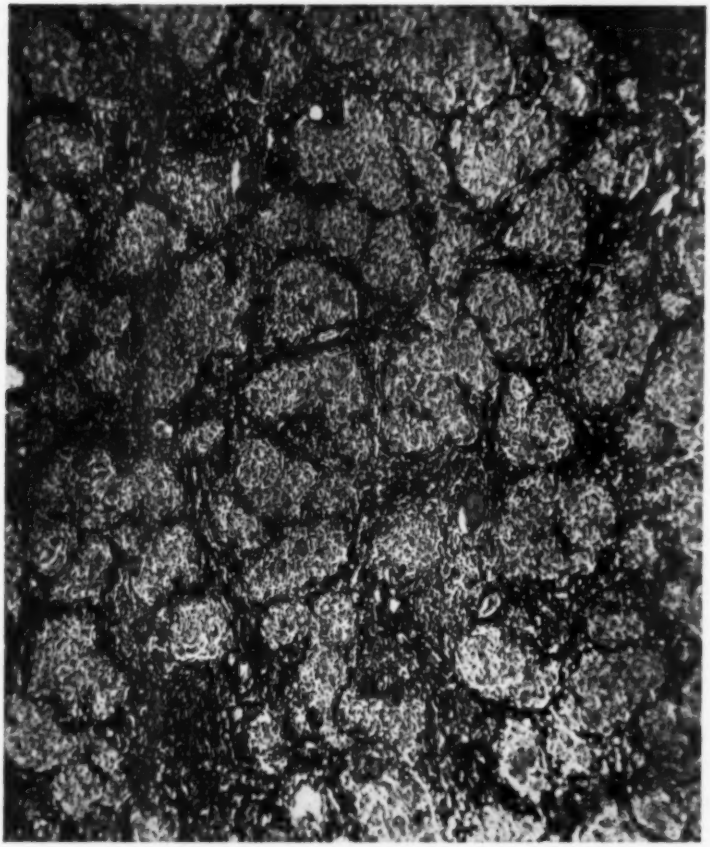

FIG. 5. Low-power magnification of lymph node, showing confluent granulomata characteristic of sarcoid.

The spleen weighed 210 gm. Its capsule was thin and smooth, its color a light rose-red. On section, the pulp was firm and uniformly pinkish-brown, and presented a coarsely granular appearance (figure 3).

Both kidneys were intensely congested, and a large area of hemorrhage was present in the pelvis of the right kidney. The urinary bladder contained a submucosal hemorrhage 1 cm. in diameter.

Along the abdominal aorta and extending throughout the mesentery and adjacent to the splenic artery were numerous hypertrophied lymph nodes, soft, moist and pinkish-white in color.

The brain showed edema and flattening of the convolutions. A large area of hemorrhage was noted in the subarachnoid space extending over the left frontal

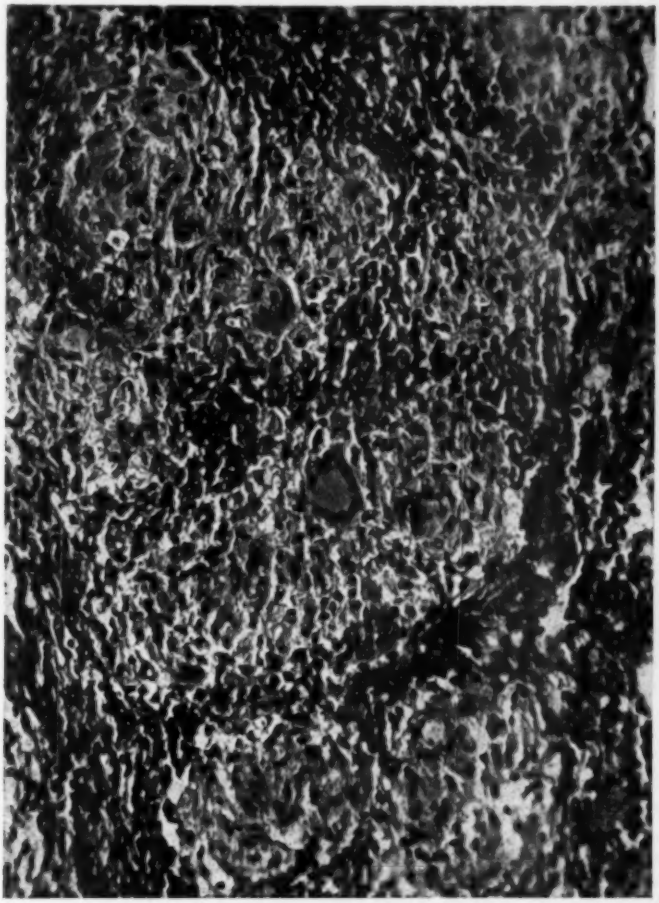

FIG. 6. Higher magnification of figure 5.

area and caudally for a distance of 6 cm., extending into the medial surface of the left frontal lobe in the vicinity of the corpus callosum. On section, a massive intracortical clot was seen to have ruptured through the junction of the first frontal gyrus with the gyrus cinguli, and also into the corpus callosum. The left lateral ventricle was

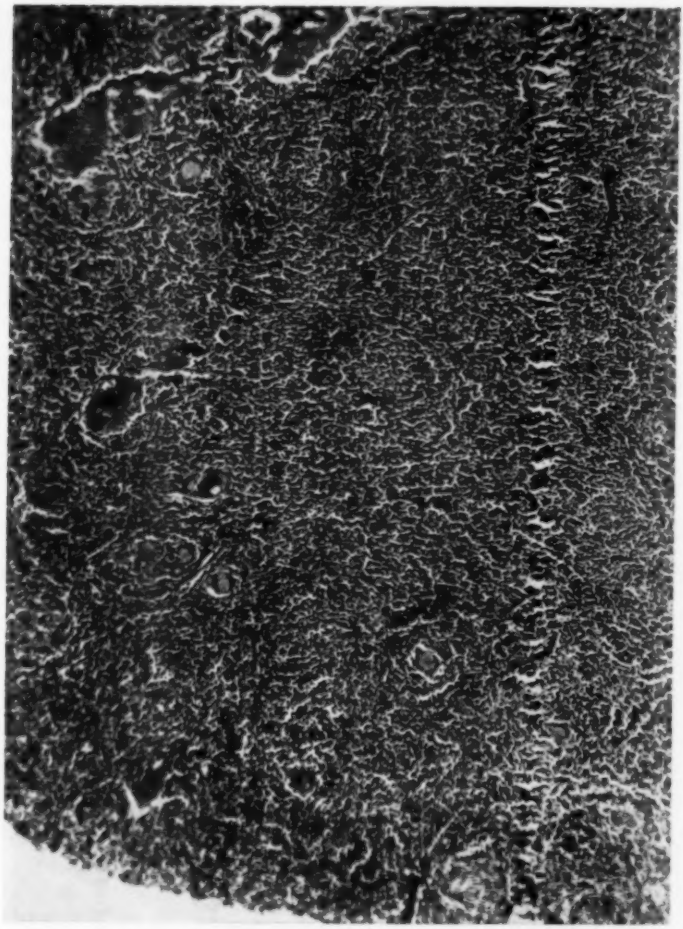

FIG. 7. Spleen, low magnification, showing numerous granulomata and solitary giant cells.

distorted and contained clotted blood. Intraventricular blood continued into the fourth ventricle (figure 4).

Microscopically, evidence of sarcoidosis was found in all lymph nodes examined and in the spleen, liver, kidneys, lungs and stomach. The lymph node involvement was that of numerous confluent, well-defined granulomatous areas, consisting of epithelioid cell proliferation and accompanied by many giant cells, these areas almost entirely replacing the architecture of the node (figures 5 and 6).

In the spleen, numerous small granulomatous areas consisting of epithelioid cells and giant cells were disturbed interstitially, principally in the reticulum. The splenic

corpuscles were small and their germinal centers were not prominent. There was no evidence of reticulum hyperplasia (figure 7). The granulomatous lesions were numerous and closely packed, but nowhere formed a large macroscopic aggregate.

In the lungs, scattered minute granulomata were noted in the peribronchial regions. In the gastric submucosa a solitary granulomatous lesion was noted.

In the kidneys numerous aggregates of lymphocytes and epithelioid cells were seen, but no true tubercles or giant cells were found.

The liver showed a moderate degree of periportal lymphocytic infiltration, and numerous small lesions diffusely scattered and consisting of epithelioid cells and occasional giant cells were seen.

No evidence of sarcoidosis was found in the sections of heart, brain, pancreas, thymus or adrenals examined.

Comment

The rôle of the spleen is, at best, poorly understood, but its dual function in the stimulation or inhibition of cell maturation has been repeatedly confirmed. Many investigators have studied the substances obtained from splenic extracts. Troland and Lee [10] obtained a very active platelet reducing factor by employing an acetone extract from spleens from cases of thrombocytopenic purpura. Later Moolton [7] demonstrated that two steroid substances, one called "thrombocytopen" because of its platelet-lowering property, and the other called by him "thrombocytosin" because of its platelet-elevating property, may be isolated from the human spleen. He also showed that from the spleens of cases of idiopathic thrombocytopenic purpura it is possible to extract "thrombocytopen" in great abundance.

In a recent well controlled and conducted experiment, Platt and Zeller [8] were able to produce thrombocytopenia in mice by injections of splenic extracts from patients with idiopathic thrombocytopenic purpura, and also from those with primary splenic neutropenia. No such change occurred when the extract from a normal spleen was used. The spleens and bone marrow of the thrombocytopenic animals at autopsy showed megakaryocytosis, but the megakaryocytes were relatively agranular and only an occasional platelet was seen. Wright, Doan, Bouroncle and Zollinger [9] recently have presented evidence to show that there is some substance or function of the spleen which enables it to remove and/or to store cells from the peripheral blood. This activity might be reflected in selective bone marrow hyperplasia and delivery. They felt that spleen withholding rather than bone marrow suppression played the major rôle in many of the hypersplenic cytopenic states.

Infiltration of the spleen by a neoplastic or granulomatous process may on occasion so alter normal splenic activity as to result in depression of one or more cellular elements. That this is due to imbalance between the cell-stimulatory and cell-inhibitory substances or the withholding properties of the organ is evident, but whether to a depression of one or a relative increase in the other is unknown at present.

Summary

Symptoms resulting from sarcoidosis of the spleen are relatively infrequent, but may take the form of neutropenia, thrombocytopenia and pancytopenia. A fatal case of diffuse sarcoidosis complicated by thrombocytopenic purpura is presented, together with autopsy findings; in this case the purpura is secondary

to hypersplenism associated with sarcoidosis of the spleen. The rôle of the spleen in the production of thrombocytopenia is briefly discussed. In each of the reported cases of thrombocytopenic purpura secondary to sarcoidosis, if splenectomy is performed a reversal of the thrombocytopenia takes place. The fatal outcome of this case by massive intracranial hemorrhage further emphasizes the need for emergency splenectomy once the diagnosis is established.

ACKNOWLEDGMENTS

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EDITORIAL

LYSOZYME IN ULCERATIVE COLITIS

Both the etiology and the therapeutic management of ulcerative colitis present many unsolved problems, and additional information bearing on this subject is badly needed. Recent observations indicating a relationship of lysozyme to this disease naturally have aroused much interest.

Lysozyme is a mucolytic and bacteriolytic enzyme (or rather a group of enzymes), first isolated and described by Fleming in egg white, and also in human tears and other secretions. Lysozyme is a crystallizable basic protein of relatively low molecular weight, optimally active at a pH of about 6.0. It causes hydrolysis of certain mucopolysaccharides, and it can be titrated by determining the reduction in viscosity it causes in solutions of such material obtained from *Micrococcus lysodeikticus* (Meyer et al.[1]). Lysozyme proved to be of no practical value as an antibiotic, as its activity seems restricted to certain groups of saprophytic organisms.

Lysozyme from human sources is very similar to that in egg white. In human stomachs surgically removed for ulcer Meyer et al.[2] found lysozyme present in high concentration in the mucosa of the duodenum, pyloric and antral regions, but low in the fundus. It is present in normal gastric juice, and Meyer found an increase, statistically significant but not very marked, in cases of peptic ulcer (except those with obstruction and vomiting). Lysozyme is also present in the mucosa of the colon, in superficial colonic mucus and in the feces. It was suggested that lysozyme causes ulceration by dissolving superficial mucus and exposing the cells to the direct attack of the digestive ferments and intestinal bacteria.

Meyer [2] carried out experiments on dogs to determine directly the effect of lysozyme on the mucosa. By allowing a strong solution of lysozyme to drip into a Pavlov pouch or into an intact stomach through a Levin tube, and by feeding the material in capsules or syrup, Meyer obtained lesions which he regarded as characteristic. The mucosa presented a "scrubbed" appearance, the superficial mucus had disappeared, and also that in the depths of the gastric glands, which could scarcely have been washed away mechanically. The mucosa showed edema, hyperemia and superficial ulcerations, especially marked in the small intestine but occasionally also in the stomach and colon. In one animal the ileum showed "a resemblance to regional enteritis."

A confirmatory series of experiments has since been reported by the same group.[3] Others, however, have stated that they were unable to produce

[1] Meyer, K., and Hahnel, E.: The estimation of lysozyme by a viscosimetric method, J. Biol. Chem. **163**: 723, 1946.

[2] Meyer, K., et al.: Lysozyme activity in ulcerative alimentary disease. I. Lysozyme in peptic ulcer, Am. J. Med. **5**: 482–495, 1948.

[3] Prudden, J. F., et al.: The effect of orally and intra-arterially administered lysozyme on the canine gastrointestinal mucosa, Am. J. M. Sc. **219**: 291, 1950.

significant lesions in colonic pouches of dogs by local application of lysozyme.[4, 5]

Meyer's conclusion that lysozyme directly produces ulceration by removing protective mucus has been seriously questioned. The concentration of enzyme used in his experiments was high, apparently higher than has been observed in human subjects, although destruction by pepsin and dilution of varying degree may make titrations of lysozyme in gastric juice deceptively low. Furthermore, neither Meyer nor Glass et al.[6] could demonstrate any mucolytic action of lysozyme in vitro on either gastric or intestinal mucus or on purified fractions of such material. No substrate in the gastrointestinal tract has yet been identified. That lysozyme plays any significant rôle in the pathogenesis of peptic ulcer is doubted by most observers.

In ulcerative colitis, however, a relationship of a high content of lysozyme to the activity of the disease is much more definite. Meyer et al.[7] found the fecal concentration of lysozyme in the acute active stage 27 times the normal, and the total fecal excretion in 24 hours was 168 times the normal. In periods of remission the fecal content was only moderately increased or even normal. These observations have been confirmed by Gray et al.[8, 9] and by Sammons.[11] There was a good correlation between the titer of lysozyme and the activity of the colitis, rising and falling with exacerbations and remissions, whether spontaneous or therapeutically induced. In regional enteritis the titer was also increased but to a less degree (six to eight times normal).[7, 12]

There is good evidence that the fecal lysozyme is formed in the colon. In a few cases of ulcerative colitis tested, the quantity in the gastric juice was normal. The content in the ileal stool after ileostomy in three severe cases was not increased. The concentration in the colonic mucus was eight times normal, but fell to normal after the fecal stream was diverted. In one severe case the concentration in the feces fell to normal after ileocolectomy. In one severe case of many years' duration with a grossly deformed and damaged colon, the concentration in the feces was but little increased. An appreciable amount of mucosa still capable of functioning seems essential for the production of lysozyme.

[4] Kirsner, J. B.: Lysozyme and ulcerative colitis, J. A. M. A. **148**: 1145, 1952 (correspondence).

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[7] Meyer, K., et al.: Lysozyme activity in ulcerative alimentary disease. II. Lysozyme activity in chronic ulcerative colitis, Am. J. Med. **5**: 496–502, 1948.

[8] Gray, S. J., et al.: Treatment of ulcerative colitis and regional enteritis with ACTH. Significance of fecal lysozyme, Arch. Int. Med. **87**: 646–662, 1951.

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[10] Grace, W. J., et al.: Studies of the human colon. I. Variations in concentration of lysozyme with life situations and emotional states, Am. J. M. Sc. **217**: 241, 1949.

[11] Sammons, H. G.: Mucinases in ulcerative colitis, Lancet **2**: 239–240, 1951.

[12] Prudden, J. F., et al.: Lysozyme titers in regional enteritis, miscellaneous tissues, microörganisms and excreta, Proc. Soc. Exper. Biol. and Med. **72**: 220, 1949.

Because of the basic character of lysozyme, Meyer et al.[2, 13] attempted to combat this with acidic detergents, using sodium hexadecyl sulfate. Nisulfazol was also used. These substances exerted a significant effect in vitro, and they also lowered the titer of fecal lysozyme in vivo in those patients who improved under treatment. Their results were confirmed by Gray et al.[14] in that there was a prompt fall in the titer of lysozyme to essentially normal levels in two to three days after the administration of a similar detergent. Gray did not, however, observe any convincing clinical improvement in these patients.

Gray et al.[8, 9] have reported a careful study of a small group of cases of ulcerative colitis while under treatment with corticotropin, cortisone, or both over a period of more than two years. These were severe cases in an active acute stage, who had been refractory to the usual measures for from one to four months. Five of six cases of ulcerative colitis and two cases of regional enteritis responded with a "significant" and "often dramatic" remission, usually within two weeks. The pathologic changes in the rectal mucosa subsided more slowly and incompletely. The roentgenographic abnormalities were less affected although "considerably improved" in three. Coincident with this there was a fall in titer of lysozyme in four to 14 days to the relatively low levels seen in cases in remission. One very advanced case gave no response of any sort. Three cases had maintained the remission for 14 to 28 months. Three others had relapsed after two to nine months but responded to a second course of treatment. There were corresponding rises and falls in titer of fecal lysozyme. Relatively large doses and prolonged courses of these hormones were required (four to six weeks). One case, in remission for three months after a second relapse, had received 11.9 gm. cortisone and 3.15 gm. corticotropin over a period of 133 days.

The question as to the therapeutic value of these hormones is beyond the scope of this discussion. The evidence at present is quite inadequate to warrant any definite conclusions, except that they do not effect a radical cure.

There can be little doubt as to the good correlation of a high titer of fecal lysozyme with activity of the disease, at least in cases in which the colonic mucosa is not too extensively destroyed. The part that lysozyme plays in the pathogenesis of the disease is much less clear. This ferment is also present in inflammatory exudates, in granulation tissue and in pus. Some increase has been reported in other types of diarrhea in which pus cells were present in the feces.[11] Moeller et al.[15] reported the local secretion of large amounts of lysozyme in dogs following cauterization of the rectal mucosa. Many have regarded lysozyme as a sequel rather than a cause of

[13] Combined Staff Clinics, Am. J. Med. **6**: 481–494 (April) 1949.

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the ulceration, and significant chiefly as an indication of the severity of the inflammation.

This may well be true in part as far as these excessive quantities of lysozyme are concerned. There is good evidence, however, that significant amounts of lysozyme are secreted by the normal mucosal cells and that this secretion is subject, to some extent at least, to nervous and possibly hormonal control. The secretion of lysozyme in dogs may be increased by the administration of mecholyl.[15] Meyer found that the gastric secretion of lysozyme was reduced 40 per cent following vagectomy. Grace et al.[10] have studied the effect of emotional turmoil on the secretion of lysozyme. In normal subjects this caused a relatively slight transient increase. In a few cases of ulcerative colitis studied, the increase was much greater and longer sustained. In one case with prolapse of the mucosa through an ileostomy, they were able to procure superficial mucus at frequent intervals, and they found that an abrupt increase in lysozyme might occur within a few minutes after the emotional stimulus.

Application to the mucosa of a pledget soaked with human tears after 24 hours caused a circumscribed area of inflammation and edema. A control with boiled tears caused no reaction. They also observed cases of ulcerative colitis in which a rise in titer of lysozyme antedated the onset of a clinical relapse.

The available evidence as to the etiologic significance of lysozyme is obviously contradictory and inconclusive. The evidence now seems to be against the view that it causes ulceration merely by removing superficial mucus. That it may injure the mucosa, perhaps in some other way, is by no means excluded. The canine mucosa and the human mucosa may react differently. Determination of the significance of lysozyme will require further studies on human subjects.

P. W. C.

REVIEWS

The Biology of Mental Health and Disease: The Twenty-seventh Annual Conference of the Milbank Memorial Fund. With 108 Contributors; Foreword by STANLEY COBB, M.D. 654 pages; 24.5 × 16 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1952. Price, $10.00.

The average internist will not be likely to read through this stout volume of 654 pages, but if he delves about in it, picking to read those Conference papers whose titles intrigue him, and if he studies with some care the foreword, the preface, and the summarization of the Conference in the last paper by Gerard, he will hardly fail to gain a new conception of present day activities in an important field of investigation relatively little known to the clinician.

The Conference was designed primarily to bring together for discussion those men who are contributing to our growing knowledge of the relationship between the structure and function of the brain and normal and abnormal mental activity. Those participating were for the most part investigators in what are commonly known as the basic medical sciences: anatomists, neurophysiologists, biochemists, neuropathologists. In addition, there were psychologists, psychiatrists, geneticists and even one internist.

In the first half of the book the papers deal chiefly with brain structure, brain metabolism, localization of functions and mechanisms of integration. The effect of loss of certain parts on mental functions is discussed. Evidence of endocrine influence on personality and behavior is presented.

The biologic aspects of mental disease are dealt with in the latter half of the volume. Experimentally induced mental disorders as well as human psychoses have been studied. Data bearing on such therapeutic measures as hypoglycemic coma, the convulsant drugs, electroshock, inhalation of carbon dioxide and nitrous oxide are presented.

The great expansion of research activity in the biological processes of the brain evidently owes much to the new technics that are becoming available, such as cytochemical analyses, tracer elements, enzymatic studies and refined methods of determining electrical changes. It is interesting to speculate how far this fresh attack upon an old problem will go to breaking down what Gerard has termed the "mind-brain barrier." This ultimate goal is still far distant. It seems probable that the more immediate value gained will be a deeper understanding of what might be called brain-body interrelationships.

It is not possible in a brief review to point out the many observations reported which have a direct interest for the clinician. It may be said, however, that in addition to acquiring broader knowledge of the biologic processes associated with mental activity he will find many stimulating suggestions as to the mechanism of the cerebral manifestations in disease.

M. C. P.

Internal Medicine: Its Theory and Practice. Originally edited by JOHN H. MUSSER, M.D. 5th ed. edited by M. G. WOHL, M.D. 1563 pages; 18 × 26 cm.; with 236 illustrations and 10 colored plates. Lea and Febiger, Philadelphia. 1951. Price, $15.00.

It is difficult to do full justice to a book of this scope in a brief review, but it seems in general that this is a rather better text than others of comparable size and range. It is for the most part well written by an impressive group of distinguished

contributors. The book has a distinctly Philadelphian flavor, as nearly half of its eighty contributors hail from that city.

As this text is primarily intended for students and general practitioners, a real effort has been made to present the clinical aspects of disease with clarity and in detail. This has been well accomplished, and the authors have simultaneously endeavored to integrate such basic sciences as physiology, biochemistry and pathology with clinical medicine.

The last edition of this work appeared in 1944, and so it has obviously been necessary to rewrite many chapters and add much new material. A striking feature of the present edition is the excellent way in which modern developments in medicine have been pithily but comprehensively summarized. Such an important subject as combined antibiotic therapy, for example, is admirably summed up in a few lines by Dr. Flippin. Similarly the subject of hypersplenism is briefly but adequately dealt with in a few short paragraphs. Such topics might easily, but inadvisedly in a text of this kind, have been dilated upon as pet subjects of the specialist authors; the temptation to make such excursions has been admirably resisted, however, and this contributes to one of the outstanding virtues of this text, balance.

In keeping with present day trends, special chapters are devoted to genetics, geriatrics, rehabilitation and psychosomatic medicine. These are adequate contributions to a work of this kind, and will probably be of real value to the student and practitioner if they are carefully absorbed. The chapter on geriatrics, contributed by Dr. Kern, is not only a practical but also a scholarly treatise. A section on the general adaptation syndrome has been contributed by Dr. Selye.

Although there are minor deficiencies—the clinical picture of cirrhosis, for example, is rather sketchily treated—the text throughout impresses one as successfully combining up-to-dateness with a sense of proportion. This is a rare and precious combination, and the book may be unhesitatingly recommended to the audience for which it is intended.

H. J. L. M.

Expert Committee on Drugs Liable to Produce Addiction. Third Report, World Health Organization Technical Report Series No. 57. 14 pages; 16 × 24 pages (paper-bound). Columbia University Press, International Documents Service, New York 27, N. Y. 1952. Price, 10 cents.

This 14 page pamphlet represents the Third Report of WHO Expert Committee on Drugs Liable to Produce Addiction. Its findings in brief are as follows:

1. At the request of the Swiss Government Ipecopan and its commercial preparations were reëxamined. Although Ipecopan powder is controlled by the 1925 Conventions the commercial derivatives mentioned contain less than 0.2 per cent anhydrous morphine and can safely be exempted from the 1925 Convention.

2. At the request of the French Government morpholinylethylmorphine was reexamined. It found that this drug is less liable than codeine to produce addiction and should be exempted from strict control in the same way as codeine.

3. The Committee announced that 50 Member States have discontinued the medical use of diacetylmorphine (heroin).

4. The Committee listed a large number of drugs and derivatives of the pethidine and methadone types, as well as others, and classified them as addiction-producing and therefore subject to control under the 1931 Convention.

5. Other subjects discussed included a statement that cannabis preparations have no medical use; a recommendation that barbiturates be controlled at the national level; control of amphetamine and its derivatives should be considered; and new facts about morphine and opium.

H. W. N.

Roentgen-Diagnostics (Volume I, Part 1, *Skeleton*). By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL, and E. UEHLINGER. First American Edition (Based on the Fifth German Edition, Revised and Enlarged), English Translation arranged and edited by JAMES T. CASE, M.D., D.M.R.E., Professor of Radiology Emeritus, Northwestern University School of Medicine; Radiologist, Highland Park Hospital; Consultant, U. S. Marine and Passavant Memorial Hospitals, Chicago, Illinois. 868 pages; 19.5 × 28 cm.; 1183 illustrations, 25 tables, and 57 charts. Grune and Stratton, New York. 1951. Price, $36.00.

Roentgen-Diagnostics is the English edition of the *Lehrbuch der Roentgen Diagnostik*, which for many years has been the most outstanding radiologic text and reference book, without equal in any language. Dr. James T. Case, with the extensive assistance of many physicians and physicists, has done a magnificent piece of work in translating this outstanding German work into a clear, easily read English edition.

Part I of Volume I is written in two sections: (1) basic principles and (2) roentgen examination of the skeletal structures.

The first section deals entirely with basic physics as applied to diagnostic roentgenography. The theory of the roentgen image, irradiation protection and the principles of fluoroscopy and photofluoroscopy are just a few of the physical problems which are discussed in an extremely clear, concise manner.

The second section is concerned with the roentgen examination of the skeletal system. The normal structures are discussed first with emphasis on the anatomy and physiology of bone growth and skeletal maturation. Following this, several well written chapters deal with the general conditions in bone, such as osteonecrosis, osteoporosis, calcium and phosphorus metabolism, and many other subjects of this nature. Finally, but much more extensive, the various bone diseases are thoroughly discussed according to their etiologies. In discussing these diseases great emphasis is placed on the anatomical and pathological considerations as related to the various roentgen findings.

This book is translated in such a fashion as to be easily read and understood. Each subject has received thorough treatment based on a good firm clinical and pathological foundation and is well illustrated with roentgenograms, photographs of necropsy material, diagrammatic sketches, charts and tables. The bibliographies are long and quite complete with up to date references from both foreign and English literature.

The only criticism which can be offered is that the roentgenographic illustrations are done in positives rather than negatives, but there are so many of these that if they were done in the negative, the cost of the book would probably be prohibitive.

The reviewer agrees wholeheartedly with one of Dr. Case's statements in the preface that, "It is our firm belief that this monumental publication, with its thorough exposition of fundamentals, and its wealth of clinical material, will prove an invaluable aid to internists, surgeons, orthopedists, urologists and other specialists in medicine, as well as to radiologists."

J. M. D.

Functional Endocrinology from Birth Through Adolescence. By NATHAN B. TALBOT, M.D., EDNA H. SOBEL, M.D., JANET W. MCARTHUR, M.D., and JOHN D. CRAWFORD, M.D. 638 pages; 26 × 17.5 cm. Published for the Commonwealth Fund by Harvard University Press, Cambridge, Mass. 1952. Price, $10.00.

This volume combines the pertinent theoretical background and the practical clinical considerations of endocrinology in early life. It covers the thyroid, adrenals, parathyroids, gonads, pituitary and pancreatic islets. In connection with the parathyroids and posterior pituitary, valuable discussions of mineral metabolism and renal function also appear. Concise and complete information for performance of the more

reliable function tests is provided along with clear data for interpretation of such tests. The present status of therapy is also well presented although in the treatment of diabetes, the therapeutic ideas, while sound, do not represent the only acceptable viewpoints.

Unusual standards of excellence are maintained in selection of text material and illustrations and in typography and composition. This is a classic which will be of great service to all who are concerned with endocrinology, particularly that in the pediatric age group.

G. E. G.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Aneurysms: The Latin Text of De Aneurysmatibus, Rome, 1745 (Opus Posthumum). By GIOVANNI MARIA LANCISI (1654–1720); revised, with translation and notes by WILMER CAVE WRIGHT, Emeritus Professor of Greek in Bryn Mawr College. 362 pages; 21.5 × 14.5 cm. 1952. The Macmillan Company, New York. Price, $7.50.

Applied Physiology. 9th Ed. By SAMSON WRIGHT, M.D., F.R.C.P., John Astor Professor of Physiology, University of London, Middlesex Hospital Medical School, etc.; with the collaboration of MONTAGUE MAIZELS, M.D., F.R.C.P., Professor of Clinical Pathology, University of London, University College Hospital Medical School, and JOHN B. JEPSON, M.A., B.Sc., D.Phil., A.R.I.C., Senior Lecturer in Biochemistry, Courtauld Institute of Biochemistry, Middlesex Hospital Medical School. 1190 pages; 22.5 × 15 cm. 1952. Oxford University Press, New York. Price, $9.00.

Basic Medical Physiology. By W. B. YOUMANS, Ph.D., M.D., Professor of Physiology, University of Wisconsin, Madison. 436 pages; 23.5 × 15.5 cm. 1952. The Year Book Publishers, Inc., Chicago. Price, $7.50.

Battle Casualties: Incidence, Mortality, and Logistic Considerations. By GILBERT W. BEEBE, Ph.D., Division of Medical Sciences, National Research Council, etc., and MICHAEL E. DE BAKEY, M.D., Professor of Surgery, Baylor University College of Medicine, etc. 277 pages; 24.5 × 16 cm. 1952. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $10.50.

Claude Bernard and The Experimental Method in Medicine. By J. M. D. OLMSTED, Professor of Physiology at the University of California, etc., and E. HARRIS OLMSTED. 277 pages; 21.5 × 14.5 cm. 1952. Henry Schuman, Inc., New York. Price, $4.00.

Brain Mechanisms in Coronary Disease: Causation, Treatment and Prevention. With Two Appendices: 1. From the Conditioned Reflex to the Science of Brain Dynamics. Paper delivered at the XVIIIth International Congress of Physiology. 2. Reflexologic Bases of Personality. Paper delivered at the Ninety-Sixth Annual Meeting of the American Psychiatric Association. By N. E. ISCHLONDSKY, M.D., Author of Brain and Behaviour, etc. 171 pages; 25.5 × 16 cm. 1952. Henry Kimpton, London. Price, 25/–.

Cancer Learning in the Medical School: A Report of Four-Years' Investigation of How and What Medical Students Learn About Cancer. By HOWARD R. BIERMAN, M.D., Associate Clinical Professor of Oncology (Medicine); LEONARD W. TOWNER, JR., Ph.D., Research Associate; DAVID W. GALLOWAY, M.A., Statis-

tician, and JAMES N. MCCLELLAND, Ph.D., formerly Instructor (Medical Education), Cancer Research Institute, University of California School of Medicine, San Francisco. 87 pages; 28 × 21.5 cm. 1952. The University of California Press, Berkeley, California. Price: While copies are available, distributed without cost to those interested in medical education.

Carbohydrate Metabolism: Correlation of Physiological, Biochemical and Clinical Aspects. 2nd Ed. By SAMUEL SOSKIN, M.D., Director of the Medical Research Institute, Michael Reese Hospital, etc.; and RACHMIEL LEVINE, M.D., Director of Metabolic and Endocrine Research, Michael Reese Hospital, etc. 346 pages; 25 × 17.5 cm. 1952. The University of Chicago Press, Chicago. Price, $8.50.

Cardiac Therapy. By HAROLD J. STEWART, M.D., Associate Professor of Medicine, Cornell University Medical College, New York, etc. 622 pages; 26 × 18 cm. 1952. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $10.00.

Circulatory Dynamics: Physiologic Studies—Modern Medical Monographs 4. By CARL J. WIGGERS, M.D., Sc.D., F.A.C.P., Professor of Physiology and Director, Department of Physiology, School of Medicine, Western Reserve University, Cleveland, Ohio. 107 pages; 22.5 × 14 cm. 1952. Grune & Stratton, New York. Price, $4.00.

Clinical Progress in Cardiovascular Disease—Modern Medical Monographs 2. Edited by HERRMAN L. BLUMGART, M.D., Physician-in-Chief, Beth Israel Hospital, etc. 143 pages; 22.5 × 14 cm. 1952. Grune & Stratton, New York. Price, $4.50.

Comparability of Statistics of Causes of Death According to the Fifth and Sixth Revisions of the International List—Bulletin of the World Health Organization, Supplement 4. 59 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; available from Columbia University Press, International Documents Service, New York. Price, 50 cents.

Diseases of the Chest. By T. ROYLE DAWBER, A.B., M.D., F.A.C.P., Senior Surgeon, U. S. P. H. S., etc.; and LLOYD E. HAWES, A.B., M.D., D.A.B.R., Radiologist at Faulkner Hospital, etc. 440 pages; 26 × 18 cm. 1952. The Williams & Wilkins Company, Baltimore. Price, $10.00.

Expert Committee on Biological Standardization: Fifth Report—World Health Organization Technical Report Series No. 56. 23 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; available from Columbia University Press, International Documents Service, New York. Price, 15 cents.

The Low Fat Diet Cook Book. By DOROTHY MYERS HILDRETH and EUGENE A. HILDRETH, M.D.; Introduction by FRANCIS C. WOOD, M.D. 160 pages; 22 × 14 cm. 1952. Medical Research Press, New York; distributed by Grosset & Dunlap. Price, $2.95.

The Pathogenesis and Treatment of Thrombosis, With a Clinical and Laboratory Guide to Anticoagulant Therapy. Modern Medical Monographs 1. By IRVING S. WRIGHT, M.D., Professor of Clinical Medicine, Cornell University Medical College, New York. 78 pages; 22.5 × 14 cm. 1952. Grune & Stratton, New York. Price, $3.00.

Pharmacology in Clinical Practice. By HARRY BECKMAN, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, etc. 839 pages; 25 × 16.5 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $12.50.

Physical Foundations of Radiology. 2nd Ed. By OTTO GLASSER, Professor of Biophysics and Head of Department of Biophysics, Cleveland Clinic Foundation, Cleveland, Ohio; EDITH H. QUIMBY, Associate Professor of Radiology (Physics), College of Physicians and Surgeons, Columbia University, New York; LAURISTON S. TAYLOR, Chief, Atomic and Radiation Physics Division, National Bureau of Standards, Washington, D. C.; and J. L. WEATHERWAX, American Oncologic Hospital and Graduate School of Medicine, University of Pennsylvania, Philadelphia. 581 pages; 19.5 × 13 cm. 1952. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $6.50.

Physics and Medicine of the Upper Atmosphere: A Study of the Aeropause. The Proceedings of a Symposium on the Physics and Medicine of the Upper Atmosphere Held at San Antonio, Texas, November 6, 7, 8, 9, 1951, sponsored by The Air University School of Aviation Medicine, Randolph Field, Texas. Arranged by The Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico. Editors: CLAYTON S. WHITE, M.D., Director of Research, Lovelace Foundation for Medical Education and Research, etc.; and OTIS O. BENSON, JR., Brigadier General, USAF (MC), Commandant, USAF School of Aviation Medicine. 611 pages; 26.5 × 18 cm. 1952. The University of New Mexico Press, Albuquerque, New Mexico. Price, $10.00.

Problems of Aging: Transactions of the Fourteenth Conference, September 7–8, 1951, St. Louis, Mo. Edited by NATHAN W. SHOCK, Chief, Section on Gerontology, National Heart Institute, National Institutes of Health, and the Baltimore City Hospitals, Baltimore, Md. 138 pages; 23.5 × 15.5 cm. 1952. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $3.00.

Rare Manifestations of Metabolic Bone Disease: Their Practical Importance—29th Annual Beaumont Lecture Delivered before the Wayne County Medical Society, February 6, 1950. By I. SNAPPER, M.D., Ph.D., Physician and Director of Medical Education, Mt. Sinai Hospital, etc. 96 pages; 22.5 × 14.5 cm. (leather-bound). 1952. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $3.00.

Recent Advances in Nutrition Research, With Emphasis on the Newer B Vitamins: Proceedings of the Scientific Sessions of the Seventh Annual Meeting, The National Vitamin Foundation, Incorporated, New York City, April 3, 1952. Nutrition Symposium Series Number 5. By A. E. AXELROD, B. F. CHOW, T. J. CUNHA, R. L. DAVIS, R. W. HEINLE, W. A. KREHL, R. W. LUECKE, E. P. RALLI, W. SCHREINER, R. B. SCHULTZ, R. W. VILTER, H. D. WALLACE, D. R. WEIR and R. W. WINTERS. 129 pages; 23 × 15 cm. (paper-bound). 1952. The National Vitamin Foundation, Incorporated, New York. Price, $1.50.

Report of the Medical Research Council for the Year 1950–1951—Committee of Privy Council for Medical Research. Presented by the Lord President of the Council to Parliament by Command of Her Majesty, June 1952. 214 pages; 24.5 × 15.5 cm. (paper-bound). 1952. Her Majesty's Stationery Office, London. Price, 6 shillings net.

Sex After Forty. By S. A. LEWIN, M.D., and JOHN GILMORE, Ph.D.; Introduction by THE REVEREND DR. RUSSELL L. DICKS, Professor of Pastoral Care, Duke University. 200 pages; 21.5 × 14.5 cm. 1952. Medical Research Press, New York; distributed by Grosset & Dunlap. Price, $3.50.

Transactions of the American College of Cardiology. Vol. I–1951. Editor: BRUNO KISCH, M.D. 138 pages; 25 × 17 cm. (paper-bound). 1952. American College of Cardiology, New York. Price, $5.00.

COLLEGE NEWS NOTES

American College of Physicians Postgraduate Courses, Autumn, 1952

The registration for the following courses has been concluded and each course had a gratifying registration:

Course No. 1, RECENT TRENDS IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE, Mount Sinai Hospital, New York, N. Y., Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-Directors; Sept. 30–Oct. 4, 1952.

Course No. 2, INTERNAL MEDICINE, SELECTED SUBJECTS, University of Pittsburgh School of Medicine, Pittsburgh, Pa., Roy R. Snowden, M.D., F.A.C.P., Director; Oct. 6–11, 1952.

Course No. 3, CARDIOVASCULAR DISEASE, Emory University School of Medicine, Emory University, Ga., R. Bruce Logue, M.D., F.A.C.P., Director; October 20–24, 1952.

The following courses are still to be given and registration is still open. Detailed bulletins of each course are available on application to the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Course No. 4, SELECTED TOPICS IN HEMATOLOGY, New England Center Hospital, Boston, Mass., William Dameshek, M.D., F.A.C.P., Director; Nov. 10–15, 1952.

Course No. 5, INTERNAL MEDICINE, CORRELATION OF NEW AND EXISTING BASIC AND CLINICAL FACTORS IN DIAGNOSIS AND TREATMENT, Presbyterian Hospital and the University of Illinois College of Medicine, Chicago, Ill., Frank B. Kelly, M.D., F.A.C.P., Director; Nov. 17–21, 1952.

Course No. 6, GASTRO-ENTEROLOGY, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., Henry L. Bockus, M.D., F.A.C.P., Director; December 1–6, 1952.

Course No. 7, INTERNAL MEDICINE, University of California School of Medicine, Medical Extension, at the Franklin Hospital, San Francisco, Calif., Stacy R. Mettier, M.D., F.A.C.P., Director; H. Clare Shepardson, M.D., F.A.C.P., Co-Director; Dec. 8–12, 1952.

Course No. 8, RECENT ADVANCES IN INTERNAL MEDICINE, University of Maryland and Johns Hopkins University Schools of Medicine, Baltimore, Md., Maurice C. Pincoffs, M.D., M.A.C.P., and A. McGehee Harvey, M.D., F.A.C.P., Co-Directors; Dec. 8–13, 1952.

American College of Physicians Regional Meetings

The following Regional Meetings have been successfully concluded:

West Virginia at White Sulphur Springs, July 25, 1952
North Dakota at Grand Forks, September 13, 1952
Western New York at Syracuse, October 3, 1952
Montana and Wyoming at Great Falls, October 10–11, 1952
Western Pennsylvania at Pittsburgh, October 11, 1952
Pacific Northwest at Vancouver, B. C., October 17–18, 1952

The following meetings are scheduled for the future. Ordinarily programs are sent only to the members in the territory covered, but physicians from other localities may obtain programs on request to the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Arizona-New Mexico, at Albuquerque, October 29, 1952
New Jersey at Newark, November 5, 1952
Southeastern at Havana, November 7, 8, 9, 1952
Kentucky at Lexington, November 29, 1952
North Carolina at Winston-Salem, December 4, 1952
Eastern Pennsylvania at Philadelphia, January 16, 1953
Colorado at Denver, February 17, 1953
Virginia, probably at Norfolk, February 26, 1953
Delaware at Wilmington, February 27, 1953
Kansas at Kansas City, March 20, 1953

Tele-Clinic No. 5, American College of Physicians

Tele-Clinic film No. 5, depicting the highlights of the 33rd Annual Session of the American College of Physicians, held at Cleveland, Ohio, April 21–25, 1952, has been concluded and is available for showing before groups of physicians anywhere in the United States. The film requires approximately 33 minutes for running and is 16 mm., black and white, sound. A number of duplicates of the film have been made. For reservations of the film, write the Executive Secretary of the College, 4200 Pine St., Philadelphia 4, Pa.

Submission of Proposals for Membership

Proposals for membership in the College must be filed at the Executive Offices sixty days in advance of action by the Committee on Credentials, and should reach the offices of the College Governors fully ninety days in advance of the meeting of the Committee.

Coming meetings of the Committee on Credentials will be held November 15, 1952; March 8, 1953; April 11, 1953.

Conference Committee on Graduate Training in Medicine

The Conference Committee on Graduate Training in Medicine is made up of two representatives from the American College of Physicians, two from the American Board of Internal Medicine, and two from the Council on Medical Education and Hospitals. Its primary duty is the passing upon hospitals for approved residencies in medicine.

The personnel of the Committee is as follows: Dr. Charles Stone, F.A.C.P., Galveston, Tex., Dr. Francis Wood, F.A.C.P., Philadelphia, Pa.—Council on Medical Education and Hospitals; Dr. LeRoy H. Sloan, F.A.C.P., Chicago, Ill., Dr. Howard Wakefield, F.A.C.P., Chicago, Ill.—American College of Physicians; Dr. Thomas Durant, F.A.C.P., Philadelphia, Pa., Dr. Walter L. Palmer, F.A.C.P., Chicago, Ill. —American Board of Internal Medicine.

The next scheduled meeting of the Conference Committee will be during the Annual Congress on Medical Education at Chicago.

First World Conference on Medical Education

The first World Conference on Medical Education will be held at the British Medical Association House, London, England, August 24–29, 1953, and will be sponsored by the World Medical Association. Details may be obtained from Dr. Louis H. Bauer, F.A.C.P., Secretary General of the World Medical Association, 2 East 103rd St., New York 29, N. Y.

Life Insurance Medical Research Fund Research Fellowships and Grants

Applications for awards available July 1, 1953, will be received by the Life Insurance Medical Research Fund as follows: (1) Postdoctoral research fellowships, until October 31, 1952. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Stipends vary from $3,300 to $4,500. (2) Grants to institutions in aid of research on cardiovascular problems, until November 15, 1952. Support is available for physiological, biochemical, and other basic research on cardiovascular problems as well as for clinical investigation in this field. Further information and application blanks may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103d Street, New York 29, New York.

The annual meeting of the American Academy of Allergy will be held at the Statler Hotel in Boston, Massachusetts, February 26, 27, 28, 1953.

Tenth Annual Meeting of the American Psychosomatic Society

The American Psychosomatic Society will hold its Tenth Annual Meeting at Chalfonte-Haddon Hall, in Atlantic City, on Saturday and Sunday, May 2 and 3, 1953.

The Program Committee would like to receive titles and abstracts of papers for consideration for the program by December 1, 1952. The time allotted for the reading of each paper will be twenty minutes. The Committee is interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all the medical specialties, and in contributions in psychophysiology and ecology.

Material for consideration by the Program Committee should be sent, in duplicate, to Dr. Sydney G. Margolin, Chairman, 551 Madison Ave., New York 22, N. Y.

American Heart Association Announces Date of Yearly Meeting

The American Heart Association has recently announced that the Twenty-Ninth Annual Meeting and the Twenty-Sixth Scientific Sessions will be held at the Hotel Chelsea in Atlantic City, April 8–12, 1953, immediately preceding the annual A.C.P. meeting. Those desiring to present papers at the Association's Scientific Sessions should submit abstracts in triplicate of the proposed presentation to Dr. Andre Cournand, Chairman of the Program Committee, c/o American Heart Association, 44 East 23rd Street, New York 10, N. Y., not later than January 1, 1953. Abstracts should not be longer than 300 words and must contain in summary form a specific statement of the results obtained or conclusions reached (not merely a statement that results or conclusions will be presented or discussed at the meeting).

"Circulation Research" Is New Publication of American Heart Association

A new bimonthly scientific journal, *Circulation Research*, devoted exclusively to reports on fundamental studies related to the heart and circulation, will be published by the American Heart Association, beginning January, 1953.

The new journal will be edited by Dr. Carl J. Wiggers, F.A.C.P., Western Reserve University School of Medicine. Among his assistants on the editorial board will be: Dr. Joseph E. Flynn, F.A.C.P., Columbia University College of Physicians and Surgeons; Dr. Louis N. Katz, F.A.C.P., Michael Reese Hospital, Chicago; Dr. Charles E. Kossman, F.A.C.P., New York University College of Medicine; Dr. Irvine H. Page, F.A.C.P., Cleveland Clinic Foundation, and Dr. Eugene A. Stead, Jr., F.A.C.P., Duke University School of Medicine.

Circulation, now in its third year of publication, will continue as a separate journal under the editorship of Dr. Thomas M. McMillan, F.A.C.P., Philadelphia, College Governor for Eastern Pennsylvania. It will concentrate more fully on clinical problems and applied research, as distinguished from fundamental research in the cardiovascular field.

A New Research Program in Medicinal Chemistry at Mellon Institute

Parke, Davis & Company, Detroit, Mich., is the donor of a new Multiple Fellowship at Mellon Institute, Pittsburgh, Pa., just announced by the Institute's President E. R. Weidlein. This Fellowship will carry on long-range investigations in synthetic organic chemistry, with general emphasis on chemotherapy and particular emphasis on the preparation of compounds for combating viruses and tumors.

The Fellowship, which was incepted on July 15, is headed by Dr. Alexander M. Moore, Administrative Fellow, since 1946 a Parke Davis specialist in the synthesis of potential drugs and in the classification of organic compounds. On his staff are three Senior Fellows: Drs. Robert S. Tipson, Alice G. Renfrew and Marcus S. Morgan. Pauline C. Piatt is a Fellow, and in the relatively near future several other scientists and assistants will be added to the group.

The American Geriatrics Society announces that effective January 1953 they will publish their own official periodical to be called *The Journal of the American Geriatrics Society*. Dr. Willard Thompson, of Chicago, is President of the Society and will edit the journal. Dr. Malford Thewlis of Wakefield, R. I., is Permanent Secretary. All physicians interested in diseases of the aging are invited to join the society. The new journal will be published for the Society by The Williams & Wilkins Company, of Baltimore, Maryland.

Postgraduate Course Sponsored by American Diabetes Association

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Chairman of the Committee on Postgraduate Education of the American Diabetes Association, has recently announced that the first formal postgraduate course ever sponsored independently by the Association will be held in Toronto, Ont., Can., January 19–21, 1953. The course, which is open to all members of the medical profession interested in the advanced study of clinical medicine and basic medical sciences related to diabetes, will be directed by Dr. Charles H. Best, Director of the Banting and Best Department of Medical Research and the Department of Physiology at the University of Toronto. Dr. Ray F. Farquharson, F.A.C.P., Professor of Medicine at the University, will be Clinical Director.

Further details concerning the course may be secured from the American Diabetes Association, Inc., 11 West 42nd St., New York 36, N.Y.

Dr. S. Marx White Honored

First Hennepin County physician to receive the St. Barnabas Bowl, an achievement award, was Dr. S. Marx White of Minneapolis, who was selected by trustees of the Hennepin County Medical Society to be recognized for the greatest medical contribution to the community. The Bowl is of the Paul Revere design, in sterling silver, ten inches in diameter. One is to be awarded annually. Funds were donated by an outstanding citizen, Mr. Charles Balles Rogers.

A year ago Dr. White received the annual distinguished award of the Community Chest and Council, of Minneapolis. Dr. White served many years as a member of the Board of Regents of the American College of Physicians, and as its President in 1931–32. He is now Professor Emeritus of Medicine at the University of Minnesota Medical School, and is 79 years of age. He has devoted considerable time to civic and scientific projects. He served in World War I in France, has been on the State Board of Health and was President thereof from 1926 to 1930; he is a member of the Hennepin County Sanatorium Commission, Director of Minneapolis Council of Social Agencies and its President from 1939 to 1941; he is Director of Hennepin County Tuberculosis Association and holds membership in many medical societies. He was one of the founders of the Nicollet Clinic.

The Comité des Hôpitaux du Québec has honored Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, Director of Professional Relations for the American Hospital Association, at the session of the Comité that took place in Quebec City, June 23–25. Dr. MacEachern was presented with a badge bearing the coat of arms of the Comité and a citation in recognition of his work in the hospital field.

In July, Dr. MacEachern gave a three-week lecture course to students in hospital administration at the University of São Paulo, Brazil.

Dr. Virgil Preston Sydenstricker, M.A.C.P., Augusta, Ga., was honored by his colleagues at the Medical College of Georgia at a testimonial dinner in June. Dr. Sydenstricker, who was cited by Dr. G. Lombard Kelly, President of the College, as the only full-time Professor of Medicine in the United States who has held the chair of medicine for thirty years, received a Certificate of Merit "for outstanding work in the field of medicine" and was presented with a gold watch from his colleagues.

Dr. Daniel H. Autry, F.A.C.P., Little Rock, has been elected Treasurer of the Arkansas Medical Society at its annual meeting.

Dr. Wallace M. Yater, F.A.C.P., a Regent of the College, was installed as President of the Medical Society of the District of Columbia on July 1. At the same time, Dr. Maurice A. Selinger, F.A.C.P., became First Vice President.

Dr. Paul D. Camp, Jr., F.A.C.P., Richmond, has recently been elected to the presidency of the Virginia Heart Association.

Dr. Jay C. Crager, F.A.C.P., Beaumont, has been elected President of the Texas Heart Association. At the same meeting, Dr. Joseph F. McVeigh, F.A.C.P., Fort Worth, and Dr. Ben H. Cooley, F.A.C.P., El Paso, were named President-Elect and Vice President, respectively.

Dr. Mary Elizabeth Bass, F.A.C.P., Professor of Clinical Medicine (Emeritus) at Tulane University, received on June 11 the Alumnae Achievement Award of the Woman's Medical College of Pennsylvania. The award was granted for "distinguished service in medical education and research, and her inspiring interest in literature by and about women in medicine."

The South Carolina Heart Association has reëlected Dr. John A. Boone, F.A.C.P., Charleston, President.

Dr. E. F. Menefee, Jr., F.A.C.P., Durham, and Dr. Charles D. Thomas, F.A.C.P., Black Mountain, have been elected President and Vice President, respectively, of the North Carolina Trudeau Society.

Col. Walter M. Bartlett (MC), USA, F.A.C.P., Decatur, Ga., has been elected President of the Thirty-Eighth Parallel Medical Society. The Society, which meets twice monthly at this latitude, is composed of medical personnel in the First and Ninth Corps Areas. Col. Bartlett is Medical Consultant at Eighth Army Headquarters.

The Texas Diabetes Association has elected Dr. E. K. Doak, Sr., F.A.C.P., Houston, to the presidency. Dr. Raymond L. Gregory, F.A.C.P., Galveston, has been named First Vice President, and Dr. Lang F. Holland, F.A.C.P., Austin, Second Vice President.

Dr. Milford L. Hobbs, F.A.C.P., Morgantown, has been elected President of the Association of Pathologists of West Virginia.

Dr. Harold Orr, F.A.C.P., Professor of Dermatology and Syphilology at the University of Alberta, Edmonton, was installed as President of the Canadian Medical Association at its last annual meeting at Banff during June.

Dr. Esmond R. Long, F.A.C.P., Philadelphia, Director of the Henry Phipps Institute for Study, Treatment and Prevention of Tuberculosis, has recently been appointed a member of the U. S. National Commission of UNESCO. He is a representative of the National Academy of Sciences, National Research Council.

Dr. Eugene B. Ferris, Jr., F.A.C.P., formerly of Cincinnati, has been appointed Professor of Medicine and Chairman of the Department of Medicine at Emory University School of Medicine, Atlanta, Ga.

Dr. James Howard Means, F.A.C.P., Jackson Professor of Clinical Medicine (Emeritus), Harvard Medical School, former Regent and President of The American College of Physicians, and Associate Editor of the ANNALS OF INTERNAL MEDICINE, received this June from the Endocrine Society the Squibb Award in recognition of his valuable contributions to endocrinology.

Col. Edgar M. Dunstan (MC), AUS, F.A.C.P., Commanding Officer of the 358th General Hospital of Atlanta, Ga., has been awarded a Third Army Certificate of Merit. The award, made at Fort Benning in July, was presented to Col. Dunstan for his "outstanding performance in preparing medical aspects for Georgia's Civil Defense plans."

Dr. Hyman I. Goldstein (Associate), Camden, N. J., has been elected an honorary member of the Mexican Association of Gastroenterology. Dr. Goldstein was also one of the speakers at the Fourth Inter-American Congress of Cardiology, held at Buenos Aires, Argentina, last month.

Dr. Hugh R. Butt, F.A.C.P., Rochester, Minn., using as his topic "Current Concepts of Pancreatitis," was one of the principal guest speakers at the annual meeting of the Medical Society of Virginia, held in the Jefferson Hotel, Richmond, September 28—October 1. Other participants included Dr. John L. Guerrant, F.A.C.P., Dr. Byrd S. Leavell, F.A.C.P., Dr. Henry B. Mulholland, F.A.C.P., Dr. Oscar Swineford, Jr., F.A.C.P., and Dr. James B. Twyman (Associate), Charlottesville; Dr. Wyndham B. Blanton, F.A.C.P., Dr. William R. Kay (Associate), Dr. William H. Higgins, Jr. (Associate), Dr. Charles M. Caravati, F.A.C.P., College Governor for Virginia, Dr. A. Ray Dawson (Associate), Dr. Lee E. Sutton, Jr., F.A.C.P., Dr. James O. Burke, F.A.C.P., Dr. Kemp Plummer (Associate), Dr. Reno R. Porter, F.A.C.P., and Dr. Kinloch Nelson, F.A.C.P., all of Richmond; Dr. Walter P. Adams, F.A.C.P., Norfolk; Dr. Julian R. Beckwith, Sr., F.A.C.P., Clifton Forge; Dr. John B. McKee, F.A.C.P., Winchester; Dr. Francis R. Whitehouse, F.A.C.P., and Dr. George B. Craddock, F.A.C.P., Lynchburg, and Dr. Edward B. Mewborne, Sr., F.A.C.P., Newport News.

The National Gastroenterological Association is holding its annual session in the Hotel Statler, New York, October 20–22. Included in the program are: Dr. Lowell A. Erf, F.A.C.P., and Dr. John R. Neefe (Associate), Philadelphia; Major I. N. Dubin (MC), USA, (Associate), Washington; Dr. Herman O. Mosenthal, F.A.C.P., and Dr. Linn J. Boyd, F.A.C.P., New York; Dr. Samuel S. Berger, F.A.C.P., Cleveland; Dr. Lay Martin, F.A.C.P., and Dr. Moses Paulson, F.A.C.P., Baltimore.

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., was one of the lecturers who participated in the Instruction Seminar of the American Congress of Physical Medicine, which was held August 25–29 at the Roosevelt Hotel, New York. He also delivered the second John Stanley Coulter Memorial Lecture on "Report on the International Congress of Physical Medicine."

At the meeting of the Colorado State Medical Society, held in Estes Park, September 9–12, Dr. Louis H. Bauer, F.A.C.P., Hempstead, N.Y., President of the

American Medical Association, discussed "Recent Developments in A.M.A. Activities." Dr. O. Spurgeon English, F.A.C.P., Philadelphia, was one of the guest speakers, his topic being "Personality Growth and Development."

Dr. Harrison F. Flippin, F.A.C.P., and Dr. John Lansbury, F.A.C.P., Philadelphia, were two of the out-of-state speakers at the annual meeting of the Medical Society of Delaware, which was held at the Rehoboth Beach Country Club, September 8–10. Their respective topics were "The A-B-C of Antimicrobial Therapy" and "The Place of Newer Drugs in Treatment of Arthritis."

Dr. Harry E. Ungerleider, F.A.C.P., New York, addressed the annual Meeting of the Northern Minnesota Medical Association on "The Insurance Aspects of Heart Disease." The meeting was held August 22–23 in Crookston.

Among the participants in the Twenty-Seventh Connecticut Clinical Congress of the Connecticut State Medical Society and the Yale University School of Medicine, which was held in New Haven, September 17–18, were: Dr. Garfield G. Duncan, F.A.C.P., Philadelphia; Dr. John H. Talbott, F.A.C.P., Buffalo, N.Y.; Dr. Earle M. Chapman, F.A.C.P., Dr. William T. Foley, F.A.C.P., Boston; and Dr. Russell L. Cecil, F.A.C.P., Dr. Currier McEwen, F.A.C.P., New York. Among those presiding at the various sessions were: Dr. Hugh L. Dwyer (Associate), Dr. William T. Salter, F.A.C.P., Dr. Arthur J. Geiger, F.A.C.P., and Dr. David H. Clement, F.A.C.P., all of New Haven; Dr. Walter Weissenborn, F.A.C.P., Dr. John C. Leonard, F.A.C.P., and Dr. Ralph E. Kendall, F.A.C.P., all of Hartford, and Dr. Paul Kunkel, F.A.C.P., Newington.

Dr. Burgess L. Gordon, F.A.C.P., Dr. Henry J. Tumen, F.A.C.P., Dr. Lewis H. Clerf, F.A.C.P., Philadelphia; Dr. Walter M. Simpson, F.A.C.P., Laguna Beach, Calif., and Dr. Frank N. Allan, F.A.C.P., Boston, are among the guest speakers at the Twentieth Annual Assembly of the Omaha Mid-West Clinical Society, which is being held in Omaha, October 27–31.

Dr. Edward F. Bland, F.A.C.P., Massachusetts General Hospital; Dr. A. Wilbur Duryee, F.A.C.P., New York University College of Medicine; Dr. Franklin D. Johnston, F.A.C.P., University of Michigan Medical School, and Dr. Irvine H. Page, F.A.C.P., Cleveland Clinic Foundation, were among the guest speakers at the Fourth Annual Meeting of the Georgia Heart Association, which was held September 12–13 in Savannah.

Dr. Hobart A. Reimann, F.A.C.P., formerly Professor of Medicine at Jefferson Medical College of Philadelphia, left about September 15 for Beirut, Lebanon, where he will spend the coming year as Visiting Professor of Medicine at the American University of Beirut.

Dr. Norbert J. Roberts (Associate) of Philadelphia has been appointed Chief Medical Officer of the Pennsylvania Railroad to direct an expanding medical program for employees.

Surgeon General Leonard A. Scheele, F.A.C.P., United States Public Health Service, has announced that 34 grants, totalling $523,993.00, have been made to aid cancer control studies and demonstrations in sixteen States, the District of Columbia, and one foreign country, Israel. The grants were made by Surgeon General Scheele on recommendation of the National Advisory Cancer Council, a group of non-government physicians, scientists, and leaders in public affairs. They will be administered by the National Cancer Institutes of Health. Fifteen of the grants are to assist new projects; all others are for continuation of previously supported projects.

Dr. F. L. McDaniel, F.A.C.P., Richmond, Va., was nominated by the President of the American Psychiatric Association, and designated by the Attorney General of the United States, to be the representative of the American Psychiatric Association at the Seventh National Conference on Citizenship, which was held in Washington, September 17–19.

Dr. A. Morris Ginsberg, F.A.C.P., Kansas City, Mo., has been promoted to the rank of Clinical Professor of Medicine at the University of Kansas Medical School. He has also been appointed Chairman of the Department of Medicine at the Menorah Hospital Medical Center, and elected Director of Medicine at the Kansas City General Hospital No. 1.

Dr. Charles F. McKhann, F.A.C.P., former Professor of Pediatrics at the Western Reserve University School of Medicine, has recently been appointed Professor of Pediatrics and Head of the Department of Pediatrics at Jefferson Medical College of Philadelphia.

Dr. Joseph J. Bunim, F.A.C.P., has accepted a full-time appointment as Chief of the Arthritis Section of the National Institute of Arthritis and Metabolic Diseases of The National Institutes of Health, U. S. Public Health Service, Bethesda, Md. Accordingly he has withdrawn from private practice and has resigned as Associate Professor of Medicine at New York University College of Medicine.

Lt. Col. Harry A. Horstman, Jr., (MC), USA, (Associate) has returned from Puerto Rico, where he has been for the past three years as Assistant Chief of the Medical Service at Rodriquez Army Hospital, and is now assigned as Chief of the Outpatient Service at the Walter Reed Army Hospital in Washington.

Dr. C. Wilmer Wirts, F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College, presented papers on "The Irritable Colon Syndrome" at the annual meeting of the Indianapolis Academy of General Practice, Indianapolis, Indiana on April 14–15, 1952, and "Pancreatic Function Tests" and "Therapy of Chronic Pancreatitis" at the Third Pan-American Congress on Gastroenterology held in Mexico City, May 11–17, 1952.

ABRIDGED MINUTES, BOARD OF COMMISSIONERS OF JOINT COMMISSION ON ACCREDITATION OF HOSPITALS

DRAKE HOTEL, CHICAGO

JUNE 13, 1952

Chairman Gunnar Gundersen called the meeting to order at 8:00 a.m.

Approval of the Minutes

The minutes of the meeting of the Commission meeting held on March 8, 1952 were approved.

Director

The Chairman announced that Dr. Edwin L. Crosby had accepted the appointment as Director of the Joint Commission on Accreditation of Hospitals and that he would begin full-time work not later than September 1, 1952 with the possibility that he might be able to take up his duties somewhat sooner.

Advisory Committee Recommendations

Housing

The Director reported that in accord with earlier action of the Commission and recommendation of the Advisory Committee, he had secured approval from the officers to enter into a rental arrangement with the American College of Surgeons for office space for the staff of the Joint Commission at 660 N. Rush Street, Chicago 11, Illinois.

Assistant to the Director

Miss Martha Johnson, R.N., M.P.H., was introduced to the Commission. It was reported that she had been employed as Assistant to the Director of the Joint Commission.

Hospital Files

The Director announced that Dr. Hawley had agreed to transfer the files of information accumulated by the hospital standardization program of the American College of Surgeons to the Joint Commission.

VOTED

That the Director prepare a resolution of thanks to the American College of Surgeons for their generous assistance in turning over to the Joint Commission all files of correspondence accumulated over the years during which the College was administering the hospital standardization program.

Orientation of Inspectors

It was reported that the Advisory Committee and the Director were making plans for an orientation course for inspectors who will be employed by member organizations

in order that the philosophy and procedure of inspection might follow a similar pattern regardless of the member organization with which the inspector is affiliated.

The following procedure was suggested:

1. That the orientation course be planned for at least one week's duration and probably would extend into a second week.
2. That the course be conducted during late October or early November.
3. That it include a "dry-run" inspection of one or more hospitals in the Chicago area.
4. That inspectors now employed by the American College of Surgeons be requested to assist Dr. Crosby in conducting the course.

Printing of By-Laws

It was reported that a number of requests have been received for copies of the by-laws of the Joint Commission on Accreditation of Hospitals. Dr. Hawley had offered to print the by-laws in the American College of Surgeons quarterly Bulletin and to make the type available for reprints or preprints of the by-laws section of the Bulletin as desired.

It was agreed that the Commission assume responsibility for general distribution of the reprints of the by-laws. In this connection, there was discussion of the need for a newsletter type of bulletin to be issued by the Commission from time to time to explain to hospitals and interested organizations and individuals the policies developed by the Joint Commission and the changes in approval standards which it is anticipated will be necessary.

VOTED

To authorize the director to publish a bulletin for distribution to interested individuals, groups and organizations from time to time as the need develops and further to instruct the director to include the By-laws of the Joint Commission in the first issue of such bulletin.

VOTED

That the Commission on Accreditation of Hospitals offer to its employees the opportunity to vote, either for or against participation in the benefits of the Social Security Act Federal Insurance Contributions.

Interim Approval of Hospitals

The Director asked advice of the Commission concerning the method for handling first approval of hospitals under the program of the Joint Commission, it being obvious that the member organizations of the Commission would be unable to inspect all hospitals presently approved by the American College of Surgeons before the end of 1952. There appeared to be general agreement that the Commission had responsibility to continue approval for those hospitals now approved until the members of the Commission had made inspections upon which continuing approval might be based.

The by-laws of the Joint Commission provide that initial accreditation of a hospital may be granted or withheld by the Board of Commissioners as a result of analysis of an inspection report or without inspection, upon unanimous recommendation of the members of the Advisory Committee.

Resignation of Acting Secretary

Mr. Norby expressed his thanks to the Commission for the privilege of having acted as its secretary during the organization period and suggested that it would be appropriate for the Commission to accept his resignation at this meeting inasmuch as the Director of the Commission who, according to By-law, acts also as Secretary of the Commission would assume his full-time duties prior to the next meeting of the Commission.

VOTED

To accept the resignation of Mr. Maurice J. Norby as Acting Secretary of the Joint Commission on Accreditation and to thank him for his assistance during the organizational period of the Commission.

VOTED

To approve the conduct of a meeting for the purpose of memorializing the establishment of the work program of the Joint Commission and further to authorize the Chairman and the Director to select the date and arrange the program for this meeting.

Adjournment

MAURICE J. NORBY,
Acting Secretary

OBITUARIES

DR. JAMES ALBERT BRADLEY

Dr. James Albert Bradley, F.A.C.P., died April 16, 1952, while on a pleasure cruise to the Virgin Islands.

Dr. Bradley was born in Jacksonville, Florida, February 22, 1900. He received the degree of Bachelor of Science in Medicine in 1925 from the University of North Carolina, and his Doctor of Medicine degree from the University of Pennsylvania School of Medicine in 1927. The following two years he spent as an Intern and Assistant Resident in Medicine at the Philadelphia General Hospital. During 1929 and 1930, he was Visiting Physician at the John Sealy Hospital at Galveston, Texas, and Associate Professor of Medicine at the University of Texas Medical Branch. Dr. Bradley then moved to New Orleans, Louisiana, where he was Assistant Professor of Medicine for a period of five years at the Louisiana State University Medical Center. Dr. Bradley practiced for a short time in Florence, South Carolina, and in 1938 moved to St. Petersburg, where he followed the specialty of Internal Medicine and Cardiology. He was a member of the staff of the Mound Park Hospital and the St. Anthony Hospital. For several years, he acted as a Consultant in Cardiology to the Veteran's Administration Center (Bay Pines).

Dr. Bradley was a Diplomate of the American Board of Internal Medicine. He had been a Fellow of the American College of Physicians since 1937. Dr. Bradley served as a Lieutenant Commander in the Medical Corps of the U. S. Navy from 1943 to 1945.

Throughout his entire career, Dr. Bradley showed unusual interest in civic affairs and the public health of his community. His untimely death is greatly mourned by all who knew him.

WILLIAM C. BLAKE, M.D., F.A.C.P.,
Governor for Florida

DR. DAVID WALTER GILLICK

David Walter Gillick, M.D., F.A.C.P., was born in St. Louis, Missouri, August 9, 1895, and died of cerebral hemorrhage at Muskogee, Oklahoma, April 30, 1952. He became a graduate of Christian Brothers College in 1915, and received his M.D. degree from St. Louis College of Physicians and Surgeons four years later.

Dr. Gillick spent his entire medical life in the service of the Indians, to whom he was devoted and whose confidence and respect he held throughout a long career. He was Medical Officer in Charge: Laguna Sanatorium, Laguna, New Mexico (1921–23); Indian Oasis Hospital, Sells, Arizona (1923–27); Mescalero Indian Hospital, Mescalero, New Mexico (1927); and Shawnee Indian Sanatorium, Shawnee, Oklahoma (1927–42).

He served as District Medical Director, U. S. Indian Service (1942–46); Area Medical Officer and Chief Medical Officer, Muskogee Area Office (from 1946), responsible for the health program of 80,000 Indians; and at the time of his death, Dr. Gillick was Chief Medical Director of the Talihina Medical Center.

Dr. Gillick, who became a Fellow of the American College of Physicians in 1938, was a Fellow of the American College of Chest Physicians, a member of the Trudeau Society, the National Tuberculosis Association and the Pottawatomie County Medical Society. He also was active in the Knights of Columbus and the Talihina Lions Club.

He was the author of several contributions on internal medicine and tuberculosis. He is survived by his wife, a son and a daughter.

WANN LANGSTON, M.D., F.A.C.P.,
Governor for Oklahoma

MAJOR GENERAL MERRITTE W. IRELAND

Major General Merritte W. Ireland, MC, retired, F.A.C.P., former Army Surgeon General and Chief Surgeon of the American Expeditionary Force in World War I, died Saturday, July 5, 1952, at the Walter Reed Army Medical Center after a long illness. He was 85 years of age.

General Ireland served longer as Surgeon General than any of his successors. He held the post from October 4, 1918, until his retirement from the Army on May 31, 1931. His term of office saw the creation of the Army Medical Center on the grounds of Walter Reed Army Hospital.

Born in Columbia City, Indiana, the son of a physician, General Ireland received his first degree in medicine from the Detroit College of Medicine and Surgery in 1890. After receiving a second degree from Jefferson Medical College in Philadelphia the following year, he was commissioned an assistant surgeon in the Army.

He served in Cuba during the Spanish-American War. Later he was assigned to the Philippines and during the Mexican expedition led by General John J. Pershing was post surgeon at Fort Sam Houston, Tex. He later went to France with Pershing where he headed the medical service of the AEF.

General Ireland was largely responsible for the development of modern concepts of field medicine during World War I and his accomplishments made possible many of the later medical achievements of World War II and Korea. Among General Ireland's awards are the Distinguished Service Medal, Commander, Legion of Honor of France, Companion of the Order of the Bath of Great Britain, and Grand Officer of Polonia Restituta, a high Polish honor. In 1945, he was awarded the William Freeman Snow Award for Distinguished Service to Humanity for his reorganization of the Army's medical service.

General Ireland was a Fellow and past President of the American College of Surgeons, a Fellow of the American College of Physicians since 1923, having served as its Governor for the Army, a Fellow of the Royal College of Surgeons of Edinburgh, President of the American Board of Medical Examiners, a member of the Council of Medical Education and Hospitals of the American Medical Association and President of the Association of Military Surgeons.

Both in his position as Chief Surgeon of the American Expeditionary Forces in France and, later, as Surgeon General of the Army for many years, General Ireland proved himself one of the great leaders of the Army Medical Service, and an unequaled administrator in the field of military medicine. His example while on active duty and his wise counsel following retirement were a source of constant inspiration to those who succeeded him as Surgeons General of the Army.

GEORGE E. ARMSTRONG, M.D., F.A.C.P.,
Major General, The Surgeon General,
Department of the Army

DR. ROBERT MARTIN MOORE, SR.

Dr. Robert Martin Moore, Sr., F.A.C.P., of Indianapolis, Indiana, died June 23, 1952, of pulmonary embolism after an illness of over two years. He was born November 18, 1884, Sommerville (Gibson County), Indiana, and graduated from Indiana University with A.B. degree (1911) and Indiana University School of Medicine with M.D. (1913). He did postgraduate study at Harvard Medical School during summers of 1920, 1921 and 1922. He served an internship at Indianapolis General (City) Hospital (1913–1914), House Resident in Medicine at Robert Long Hospital (1914–1915) and entered the private practice of Internal Medicine in Indianapolis (1915–1917). He then entered the U.S. Army in World War I as first lieutenant and

became captain (MC) A.E.F. During this time he became physician in charge of Hospital D, Base Hospital 32, France (September, 1917–July, 1919).

On return he became Associate in Medicine, and in 1934 Associate Professor of Cardiovascular Renal Diseases, Clinical Professor of Cardiology (1938), and Professor of Clinical Cardiology (1949). He established the cardiac clinic of the Indianapolis General Hospital in 1922, to which he gave his devoted services and remained its distinguished leader during his active life. He was chairman of the Medical Service at the Indianapolis General Hospital (1937). Other hospital affiliations included Methodist Hospital, of which he was Chairman of the Medical Advisory Board, visiting staffs of Robert Long Hospital, James Whitcomb Riley Hospital for Children, St. Vincents, St. Francis and Indiana Christian Hospitals.

In addition to memberships in state and local societies, Dr. Moore was a member of Delta Tau Delta, Nu Sigma Nu, American Association for the Study of Goiter and the Central Society for Clinical Research. He had been vice president of the Indianapolis City Hospital Staff Society, president of the Methodist Hospital Clinical Research Society and president of the Indianapolis Medical Society (1938). He was a member of the Advisory Council of the American Heart Association and chairman of the Committee on Cardiac Clinics (1941) and a member of the Activities Committee (1941). He became a Diplomate of the American Board of Internal Medicine (1937) and had previously been elected to the American Congress on Internal Medicine (1924). He became a Fellow of the American College of Physicians in 1927 and was Governor for Indiana (1932–49). During his term of Governor for Indiana, there developed an interest in the American College of Physicians unprecedented to that time.

His son, the late Robert M. Moore, also a captain in the Medical Corps, was the first Indianapolis man killed in the Korean War (July 16, 1950). Another son, Phillip V. Moore, is a World War II Veteran.

One of Dr. Moore's most outstanding attributes was his unerring devotion to his family, to his friends and to all those things contributing to the advancement and practice of medicine. As a teacher he aroused an enthusiasm to a degree seldom attained, and young men eagerly followed him. To his patients he showed a kindliness and inspired a confidence that never lagged. To his associates, he was a leader, a wise counsellor and a devoted friend. His memory will long endure.

J. O. Ritchey, M.D., F.A.C.P.,
Governor for Indiana

DR. HAROLD WILLIAM PALMER

Harold William Palmer, A.B., M.D., F.A.C.P., was born in Anderson County, Kansas, January 13, 1899, and died at his home in Wichita, Kansas, of coronary occlusion on July 12, 1952. Survivors include his widow, Mrs. Jean Palmer, and one daughter, Joann.

Dr. Palmer received his A.B. degree from University of Kansas in 1922 and his M.D. degree from the same institution in 1925. He interned at Cleveland City Hospital, 1925–1926, and served as Resident in Medicine in the same institution, 1926–1927. Following three years of general practice he went to Vienna for postgraduate study in 1930, and upon his return entered the practice of Internal Medicine in Wichita.

He was a member of the Staff of Wichita and Wesley Hospitals and served as Consultant at the Veterans Administration Hospital and at the Wichita Air Force Base Hospital. He became a Fellow in the American College of Physicians in 1934; Diplomate of the American Board of Internal Medicine, 1939; and served in the U. S. Army Medical Reserve Corps with active service in the South Pacific area during

World War II from June, 1942, until January, 1946, reverting to inactive status as a lieutenant colonel in 1946.

Dr. Palmer took an active interest in all things medical and served the Sedgwick County Medical Society in several offices. He was a member of Nu Sigma Nu Medical Fraternity. He was an active member of the Kansas State Medical Society and the American Medical Association.

Through the years, Dr. Palmer was a consultant for many friends in this area, and his kindly counsel, both medical and personal, will be missed greatly. The American College of Physicians, and especially the membership in Kansas, have lost a valuable member, colleague, and friend.

FRED J. MCEWEN, M.D., F.A.C.P.

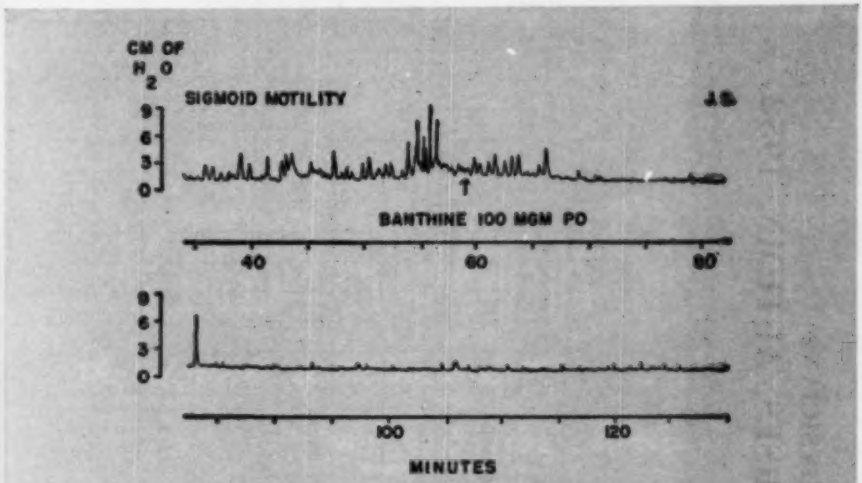
DR. AUGUST FERDINAND RIES

Dr. August Ferdinand Ries, F.A.C.P., died in Baltimore on January 3, 1952, after nearly fifty years of medical practice. Though he suffered rheumatic valvular disease, this handicap did not deter him in the performance of his duties. By preference, Dr. Ries never abandoned a "general practice." His fluent knowledge of the German and Hebrew languages endeared him to his local community of South Broadway, and it was a great asset in his work as family doctor, adviser and friend.

Born in Baltimore on December 25, 1875, Dr. Ries attended local schools and in 1903 graduated from the College of Physicians and Surgeons of Baltimore. In addition to conducting a private practice, Dr. Ries taught osteology at the College of Physicians and Surgeons until 1916. He was greatly interested in the organization of the South Baltimore General Hospital, and for years he was Senior Visiting Physician there. At the Church Home and Hospital, he was an Associate Physician and he was a member of the Courtesy Staff of the Mercy, Bon Secours, and Sinai Hospitals. Dr. Ries was a Diplomate of the American Board of Internal Medicine. In 1930 he was elected a Fellow of the College.

Among his medical colleagues, Dr. Ries was retiring but was popular and highly regarded. To all he was known as conscientious and sincere.

R. CARMICHAEL TILGHMAN, M.D., F.A.C.P.,
Governor for Maryland



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1. Kern, F., Jr.; Almy, T. P., and Stolk, N. J.: Effects of Certain Antispasmodic Drugs on the Intact Human Colon, with Special Reference to Banthine (β-Diethylaminoethyl Xanthene-9-Carboxylate Methobromide), Am. J. Med. *11*:67 (July) 1951.

2. Lepore, M. J.; Golden, R., and Flood, C. A.: Oral Banthine, an Effective Depressor of Gastrointestinal Motility, Gastroenterology *17*:551 (April) 1951.

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REFERENCES: 1. Dey, T. J. et al.: Proc. Staff Meetings Mayo Clinic 21:497, 1946. 2. Hoagland, R. J.: Am. Jl. Med., 9:272, 1950. 3. Smith, R. T.: J. Lancet, 70:192, 1950.

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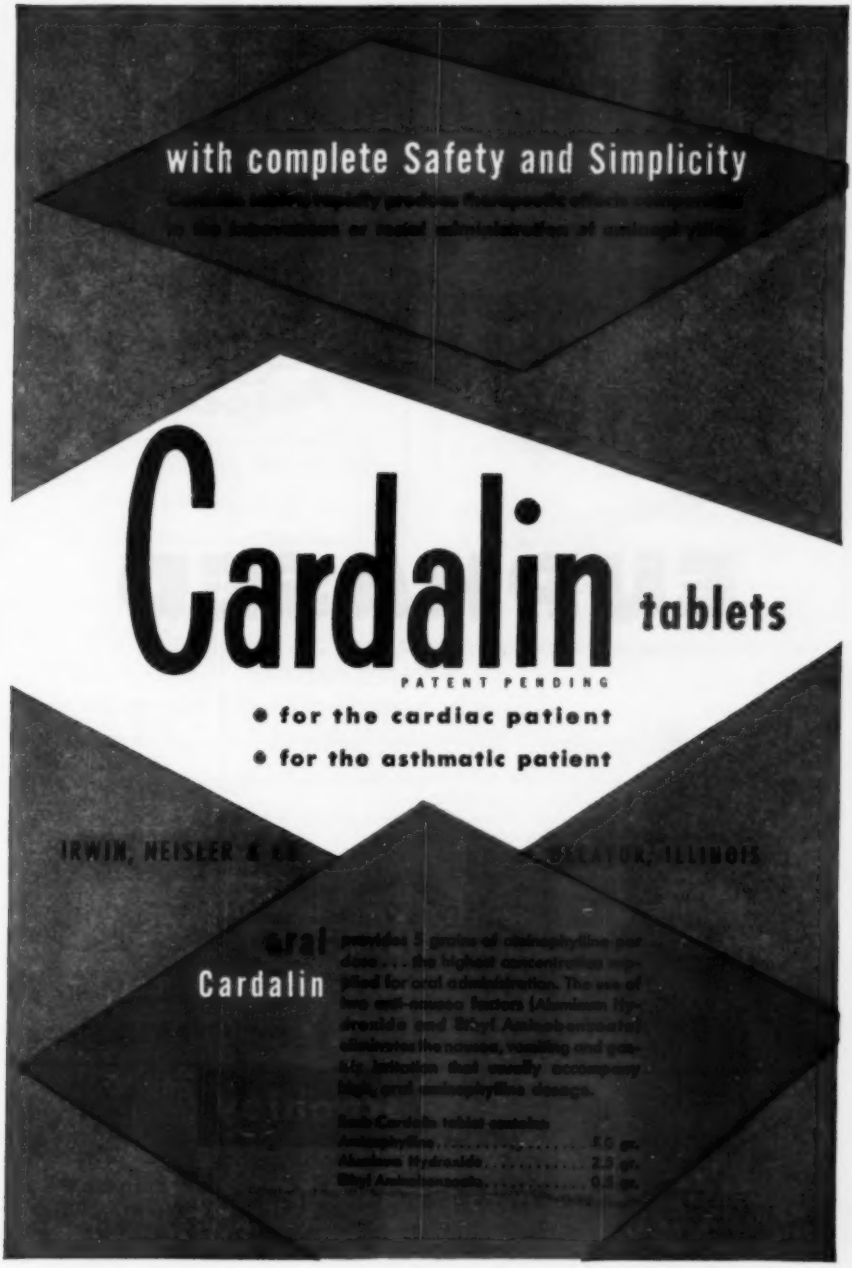
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